S. HRG. 99-367

DRUG EXPORT REFORM

HEARING

BEFORE THE

COMMITTEE ON
LABOR AND HUMAN RESOURCES
UNITED STATES SENATE

NINETY-NINTH CONGRESS

FIRST SESSION

ON

PROPOSED LEGISLATION TO AMEND THE FEDERAL FOOD, DRUG AND COSMETIC ACT TO AUTHORIZE THE EXPORT OF NEW DRUGS AND BIOLOGICALS NOT YET APPROVED IN THE UNITED STATES TO COUNTRIES THAT HAVE APPROVED THEM

JUNE 5, 1985

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DRUG EXPORT REFORM

WEDNESDAY, JUNE 5, 1985

U.S. SENATE,
COMMITTEE ON LABOR AND HUMAN RESOURCES,
Washington, DC.

The committee met, pursuant to notice, at 9:39 a.m., in room SD-430, Dirksen Senate Office Building, Senator Orrin Hatch (chairman of the committee) presiding.

Present: Senators Hatch, Kennedy, Thurmond, Metzenbaum, Simon, Kerry, Grassley, Quayle, and Dodd.

OPENING STATEMENT OF SENATOR HATCH

The CHAIRMAN. This committee will come to order.

This morning the committee is pleased to welcome several panels to address the question of drug export reform. Through an apparent drafting error in a last-minute amendment to the 1938 reenactment of the Food, Drug, and Cosmetic Act, the export of "new drugs" under the act was placed on a different footing than other products subject to the act. As a result, "new drugs," which account for the great majority of prescription pharmaceuticals, cannot be exported from the United States unless they have been approved by the Food and Drug Administration. This ban applies even when the drug is perfectly legal in the importing country.

As might be expected in the case of an unintended policy, this restriction is unique. No other substances, including admittedly hazardous chemicals, are subject to such restriction. In such other cases, the United States instead relies on notification of the importing country of its findings, but allows export to that country if the substance can lawfully be marketed there. The same is true for all pharmaceuticals which are not considered "new drugs," such as antibiotics and vaccines.

That the importing country's viewpoint should be the basic consideration was confirmed as recently as 1976, the last time Congress expanded the jurisdiction of the Food, Drug, and Cosmetic Act. In explicitly bringing the broad range of medical devices under FDA review, Congress did not adopt the 1938 "new drugs" position but rather made export essentially dependent on whether the products are legal in the importing country.

Also, as one would expect in the case of an unintended policy, the United States, anomalous restriction on drug exports is not shared by any other nation nor is it in conformity with international policy. Indeed, the policy of the United Nations recognizes the right of all countries to have access to the full range of pharmaceuticals and places on the importing country the responsibility for protecting its consumers, with the technical assistance of foreign or international agencies where needed.

Of course, this committee is not a stranger to the subject of drug export reform. In June of last year, we held hearings on the issue, and the House followed with hearings in July. Also, in July, drawing on our hearing, I introduced S. 2878, the Pharmaceutical Export Reform Act of 1984. This bill would have partially relaxed the current ban by allowing the export of pharmaceuticals not yet approved by FDA under a series of conditions designed to ensure the safety of these drugs.

I hasten to add that the bill did not permit the export of drugs which have been banned or denied licensing, but only those on which FDA has not yet acted. It was endorsed by the pharmaceutical industry and by the FDA. The bill's safeguards were stronger than those enunciated by Dr. Dunne of the World Health Organization in his July House testimony. However, the movement of this bill, as a number of others, was affected by other issues we faced last year, and we did not have the occasion to consider it in markup.

With this hearing, we are returning to the review of what I feel is our current mistaken, unintended, and unfortunate policy. As has been widely noted, the U.S. ban does not really affect which pharmaceuticals reach foreign consumers, since any drug may lawfully be produced abroad, including in Soviet bloc countries and others, which do not recognize patent protections, and may be marketed without restrictions around the world.

But the consequences for our economy are real. I would like to refer to a series of tables. The first (table I), compiled from data provided at our hearing last year, illustrates some very distressing trends for the .US. pharmaceutical industry.

Between 1960 and 1980, the last year for which we have accurate data, there has been a marked downward trend in the U.S. share for every indicator: the world pharmaceutical market, world pharmaceutical exports, new drugs entering clinical trials, and pharmaceutical production located in the United States. U.S. pharmaceutical firms lead the world industry today as they always have.

And we are not trying to sound the death knell for that industry. But it is important for us to realize that our industry is not alone in the world, and the competition is increasingly vigorous. We can safely say that our industry's position as the world leader has become increasingly tenuous. Drug export restrictions have, in part, contributed to this decline.

Now, let me refer to the second table (table II) over on this side of the room. It is a little difficult for you to read, but we have them here so you can look at them before and after the hearing and during the recess.

[Tables I and II follow:]

Tenuous Position of U.S. Pharmaceutical Leadership

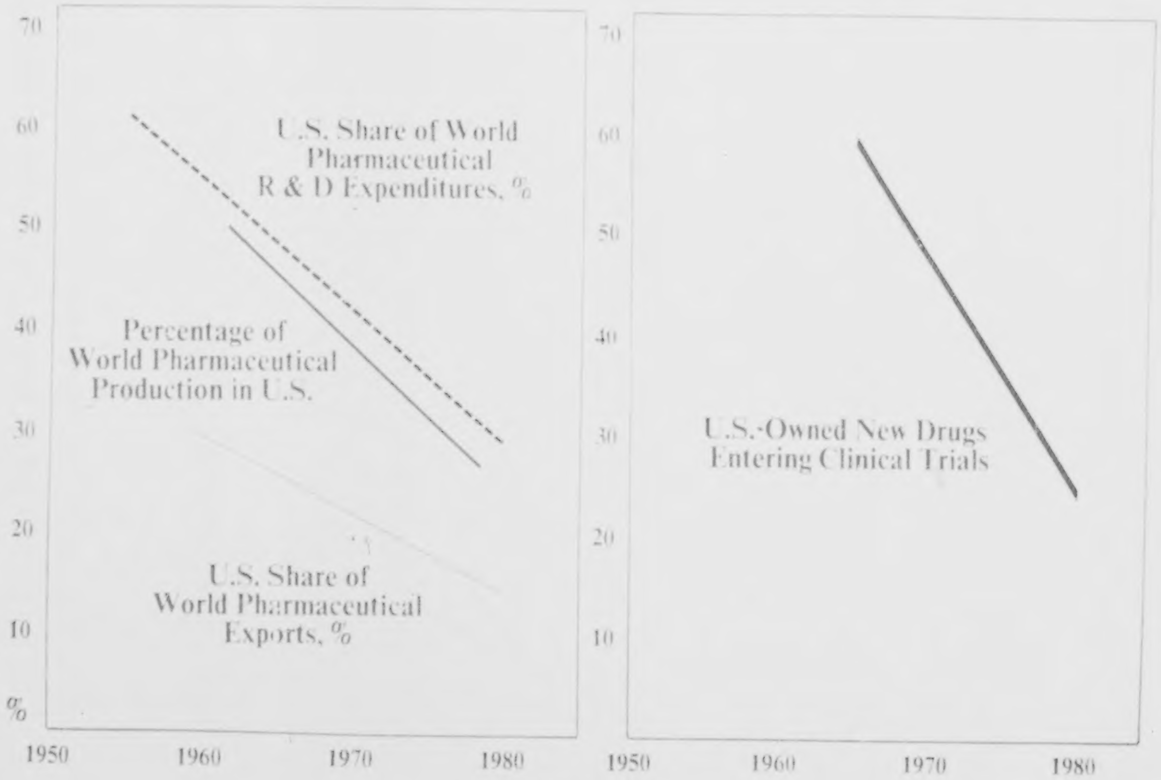

TABLE I

*1980 - Latest Data Available

Fifth-Year Economic Impact of Reducing Drug Export Restrictions

Positive by any Measure

	Maximum Potential Impact *	Conservative Estimate	Low Estimate **
Increase in Annual Export Sales	$1.76 billion ($360 million on drugs not yet FDA approved)	[illegible]	[illegible] million
Increase in U.S. Trade Surplus for Drugs***	[illegible]	[illegible]	[illegible]
Increase in Incremental Capital Investment	$400 million	$91-$114 million	[illegible] million
Annual New Jobs			
(Based on 2,000 Jobs per $1 Billion [illegible] [illegible])	40,500	9200-11,500	5000
(Based on Labor Institute's Estimate of [illegible] Jobs per $1 Billion Exports)	20,115	4,571	2,492

TABLE II

*American [illegible]

**Labor Institute 1984 figures based on 1983 [illegible]

***Relative to 1983 U.S. [illegible]

The CHAIRMAN. At last year's hearing we were provided with data relating to the economic impact of easing drug export restrictions. A study done by American Cyanamid's Lederle Laboratories outlined what I would like to call the best case scenario:

In the left-hand column, if drug export legislation were passed, after 5 years the U.S. pharmaceutical industry would experience a whopping $1.76 billion annual increase in exports, 40,000 new jobs would be created annually, and the balance of trade would be shifted in our favor. Cyanamid itself stated that these figures represent the maximum potential impact. In the right-hand column, another study taking a very skeptical view arrived at increases of $217 million in annual exports and 2,482 jobs. The true impact of drug export legislation undoubtedly lies somewhere in the middle.

Using an intermediate moderate set of figures based on projected exports of new drugs not yet approved in the United States, plus a small amount assuming slight relocation of existing foreign production, we reach a result of $400 to $500 million additional each year.

In light of our currently severe balance of payments deficit, this is a very significant sum, and does not even include a component for a reduction in imports resulting from the statutory change. Based on $400 to $500 million in increased exports, we could reasonably expect an increase in capital investment of $90 to $114 million and the maintenance of somewhere between 8,000 and 12,000 new jobs each year. But whatever assumptions one selects, the bottom line is clear: any way we slice it, the impact of export reform is very positive for the economy and for our workers in this industry.

The final graph (table III) on the right-hand side reinforces the deterioration of the U.S. pharmaceutical exports and imports situation. Imports have increased sharply over the last 2 years, highlighting a 5-year trend, while increases in exports have begun to level off. Thus we see a clear decline in net exports. Clearly, in terms of our balance of trade problems, we would like to see a reversal of this disturbing trend. Driving our own plants overseas only contributes to this problem.

[Table III follows:]

Foreign Trade on the United States in Medicinals and Pharmaceutical Preparations, 1979-1984

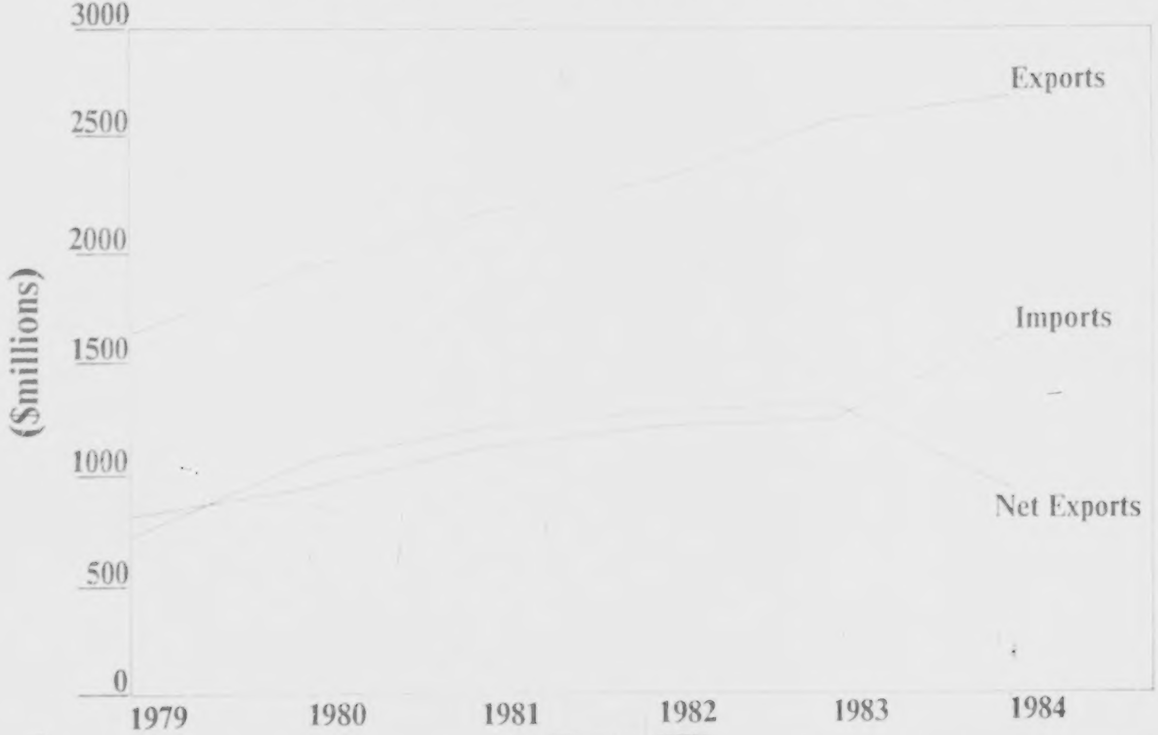

TABLE III

Source: U.S. Department of Commerce

The **Chairman**. The burden of present policy falls with particular weight on the biotechnology industry. We have two witnesses this morning who I believe will state their case more fully, but let me observe in passing that biotechnology holds the exciting prospect of future progress we can now scarcely imagine. It promises to revolutionize disease treatment and pharmaceutical development, food production, waste disposal, and many other fields.

Blessed by a unique combination of scientific genius, financial resources, and entrepreneurial spirit, the United States is currently the world leader in this beneficial technology. But we find ourselves in danger of losing that position through the forced export of critical biotechnology to companies of other nations, as a result of our inability to export as yet unapproved pharmaceuticals.

In this regard, I would like to add to the list of those supporting export reform the United States Steelworkers, Local No. 12075, of Midland, MI, representing 2,500 pharmaceutical workers. I have recently received a statement from them which I will, without objection, place in the record at the end of my statement. But I would like to read two excerpts.

> The members of Local 12075 are employed by the Dow Chemical Company and are engaged in the manufacture of pharmaceutical active ingredients for Dow and its wholly owned subsidiary Merrell Dow Pharmaceuticals, Inc. In the past ten years, the employment at Dow Midland location has decreased from 5,000 to 2,500 employees in the bargaining unit.
>
> We are interested in keeping this work in the United States, especially in Midland, Michigan. Also, we feel that this legislation would generate new jobs.
>
> Our understanding of the proposed legislation is that it would allow U.S. manufacturing sites to be used to manufacture and export these unapproved drugs to countries which have already approved the product for sale. We view the proposed legislation as enabling U.S. workers to be on an equal footing with foreign workers in that we will at least be one of the countries on the list as a possible source of supply.
>
> We have been made aware of the fierce competition among governments to get companies to manufacture in, and export from, their countries. It makes good sense to us to allow U.S. sites to be among the possibilities. A site that is not even on the list of possibilities obviously cannot be chosen in a manufacturing sourcing study.

It is against this background that I welcome our witnesses today, and I am sure their comments will be illuminating and I want to thank them in advance for their testimony.

Now, I haven't even referred to the health benefits to foreign consumers which would accrue from a drug export reform package. All the talk about jobs, all the talk about developing trade, all the talk about business aside, that is all important, but really the most important benefits from a drug export bill I think will accrue to people who need this type of legislation to help in the countries that just simply do not benefit from our research as much as they will if we have a reasonably worded, intellectually intelligent and compassionate drug export reform bill.

So I look forward to this hearing today and I hope that we can in a bipartisan way develop a bill that will be acceptable to industry, to consumers, to everybody concerned, and to people worldwide that will be of considerable aid to consumers worldwide, and particularly to the benefit of our country as well.

At this point we will turn to Senator Kennedy and take his statement.

Senator **Kennedy**. Thank you very much, Mr. Chairman.

We are here this morning to discuss the export of the pharmaceutical products and biologics.

The current U.S. policy on the export of pharmaceutical products is a restrictive one. No export or manufacture of pharmaceutical products is permitted without a complete "new drug approval" by the Food and Drug Administration. The only exception is drugs used for investigational purposes.

Though this policy has been highly responsible, it has also substituted the regulatory authority of the FDA for regulatory agencies in other countries with their own high standards and unique priorities. In addition, where medicines have been approved more quickly in other countries, this policy has encouraged American pharmaceutical companies to establish plants overseas.

This issue has been highlighted recently by biotechnology companies which comprise a new and promising growth industry. The United States currently leads the world in biotechnology. However, because of the new entry of biotech firms to commercial markets and the smaller size of these companies, they are unable to locate production centers overseas.

Meanwhile, foreign demand for biologic products and more rapid approval of some products is creating mounting pressure to move production overseas. Some companies are considering exporting their technology, rather than wait out FDA approval. In a few cases, this has already happened.

While maintaining responsible policy on pharmaceutical export is of the utmost importance, the existence of sophisticated regulatory systems in a number of foreign countries makes it possible to think in terms of loosening our current export restrictions. It is true that new drug approval requirements of the FDA have been the most comprehensive in the world. But in recent years, a number of countries have revised their protocols so they increasingly resemble those of the FDA. Experts have judged their systems to be similar in quality to the FDA.

In this context, allowing export of American pharmaceuticals to specific countries based on their own internal regulatory decisions is reasonable. Genentech and three pharmaceutical companies have made proposals along these lines. They will describe their approach in testimony this morning. Their ideas are a worthwhile starting point.

In my view, additional safeguards are needed to guarantee protection to the public and to avoid undermining the regulatory authority of the Food and Drug Administration.

Three specific suggestions I would like to make are:

First, these products must not end up in Third World countries that do not have adequate infrastructure or public awareness to use them properly;

Second, any reworking of food and drug law must not serve to bypass FDA regulators. FDA approval should be pursued to completion; and

Third, the Secretary of Health had Human Services must have the ability to approve each request for export and to discontinue export should concerns arise about the safety or effectiveness of any such product.

Many concerns were expressed at our hearing last year about the issue of "dumping" of pharmaceutical products on the Third World. Questions were raised about labeling and marketing practices of the industry as well as the ability of some countries to handle medications properly.

American firms state that such practices have been eliminated by U.S. companies. Mr. Humphrey Taylor, of Louis Harris Associates, will be joining us this morning to describe a possible route by which a survey of such practices might be accomplished in the Third World. Such information would also provide us with a data base for further initiatives of drug export.

I look forward to the testimony of all our expert witnesses today. I regret that I will not be able to remain during the course of the hearing. I, like the chairman of this committee, am a member of the Judiciary Committee and, with Mr. Reynolds' nomination up, will have to leave later in the morning.

I want to thank the Chair.

The CHAIRMAN. Thank you, Senator Kennedy.

Senator Thurmond?

Senator THURMOND. Thank you, Mr. Chairman.

Mr. Chairman, it is a pleasure to be here this morning to receive testimony on drug export reform. I welcome Commissioner Young of the Food and Drug Administration and the other distinguished witnesses who are here today.

Recently, I introduced the Textile and Apparel Trade Enforcement Act of 1985. In my statement introducing that legislation, I said that one of the chief reasons imports are capturing larger shares of our domestic market is because foreign manufacturers do not compete with our domestic textile/apparel producers on a level playing field.

I am concerned that a similar situation is occurring in our domestic pharmaceutical industry. Under current law, pharmaceuticals may not be exported for sale abroad unless they have already been approved by the Food and Drug Administration. This restriction applies despite the fact that the particular drug has been approved in the country of destination.

An example of problems resulting from the current law is found in my home State. Norwich Eaton Pharmaceutical, which operates their primary manufacturing plant in Greenville, SC, has the capacity to manufacture certain drugs which are in demand and have been approved by foreign countries. In order to apply this need, pharmaceutical manufacturers, like Norwich Eaton, must build plants and manufacture abroad, to the detriment of the American economy.

The huge trade deficit of our country is a major crisis which Congress must address immediately through appropriate legislation. In a recent report, the Commerce Department has predicted that, although we currently enjoy a positive balance of trade in the pharmaceutical manufacturing industry, if the present trend continues, a negative balance of trade will exist by the end of 1986.

The testimony presented today will allow this committee the opportunity to carefully examine the need for legislation which will provide adequate health safeguards, and also create American jobs.

The full Judiciary Committee is conducting hearings this morning and, as chairman, I must preside. Hwever, I look forward to reviewing the testimony of these fine witnesses and thank them again for their appearance today.

Thank you, Mr. Chairman.

The Chairman. Thank you, Senator Thurmond.

We will now enter into the record the opening statements of Senators Quayle, Metzenbaum, and Kerry.

[The opening statements of Senators Quayle, Metzenbaum, and Kerry follow:]

Opening Statement of Senator Quayle

Good morning, ladies and gentlemen. I am pleased to be here today to listen to your thoughts on the important subject of drug export reform.

Last year, in conjunction with our distinguished chairman, Senator Hatch, I cosponsored S. 2878, legislation designed to reform our Nation's troublesome policy on drug exports. Currently, our laws impose an absolute ban on the export of all drugs manufactured in the United States unless they have been approved by the Food and Drug Administration. It is worth noting that such a prohibition does not exist for the export of antibiotics and vaccines. S. 2878 would have had the effect of ameliorating this restrictive policy on drugs by permitting their export with certain important safeguards.

This bill served as the focal point for generating significant discussion on the need for drug export reform and sharpened the issues we must now address in terms of resolving the future of our Nation's policy in this area. Specifically, these issues relate to U.S. jobs, the export of U.S. knowledge and technology, our Nation's international competitive position, the health needs of other countries including Third World nations, and public health and safety concerns. The issue is not whether drugs not approved by the Food and Drug Administration will reach foreign markets. We all know that such drugs may be produced and distributed abroad. The question is whether or not the U.S. economy will be able to reap the benefits involved. I am hopeful that we can all work together to resolve these matters so that we may enact legislation that will work toward keeping the economic benefits of U.S. research and technology—the jobs, the plants, and tax base—at home.

Moreover, as we consider reform of our drug export laws, it is vitally important to remember that time and technology have not stood still. While the United States still retains the lead in pharmaceutical development, this lead is not as secure as it once was. It is important to work to retain our competitive edge and I believe a reform of our drug export laws will help us do this. It is also essential that the United States remain in the forefront of new discoveries. The biotechnology industry is clearly a case in point and I think our witnesses today will address this issue and outline our potential for progress.

I would like to commend Chairman Hatch for holding this hearing. I look forward to working with him and my other colleagues on reforming our drug export policy in an expeditious and responsible fashion.

Opening Statement of Senator Metzenbzaum

Mr. Chairman today we will hear from the pharmaceutical industry on drug exports. They've got an idea. We're told it'll bring jobs, technology, investment to our economy. Bring back jobs from overseas. Help our companies compete on equal footing with foreign firms.

It will achieve all these goals simply by allowing U.S. firms to export unapproved drugs.

Mr. Chairman, if it all sounds too good to be true, that's because it is.

If this proposal ever sees the light of day, the health and safety of foreign consumers will be jeopardized, the "Made in America" label will be tarnished, and our international reputation as a trading partner will be undermined.

This proposal incorporates a dangerous double standard for drug safety. Drugs which have not completed the FDA approval process for safety and efficacy will be exported to foreign countries. The message we will send to the rest of the world is clear and unambiguous: These drugs aren't good enough for us, but they're good enough for you.

The bill was opposed by groups as diverse as the United Methodists and the International Chemical Workers Union.

But the drug industry is back again knocking on Congress door. They have their lobbying machine oiled and they are confident—confident that the health and safety of foreign consumers is not as important to Members of this Congress as the bottom line on the profit sheet of America's most profitable industry.

Confident that this Congress will buy their argument that the FDA takes too long to approve drugs. Even though the Secretary of Health and Human Services recently announced regulations which will speed that process dramatically. Regulations she hailed as the most important in 20 years.

If this proposal were law, those drugs could have been produced here and borne the label "made in the U.S.A."

The tragedy of Bhopal focused this Nation's attention on U.S. corporate responsibility abroad. How do you think this Nation would be judged if one of these unapproved drugs slipped through causing death and injury abroad while American citizens were protected because we only allowed the drug to be produced for export?

The best safeguard is the one we have right now—if a drug is not proven safe and effective, don't export it.

I know the counterargument. All the other major drug producing countries do it, why shouldn't we? I respond with a question. Since when did this great Nation play follow the leader on questions of international morality?

We may have the strictest standards for safety among all nations, but I don't hear anyone advocating less thorough standards for the FDA. What I do hear people saying is let's circumvent the process for drug exports. After all, as long as we don't have to risk using drugs, who cares?

Finally, Mr. Chairman, I am aware that a compromise proposal has been advanced by Genentech which would restrict the export of unapproved drugs to countries on the approved list. Major problems are posed by this new proposal. There are no protections against reexport problems with labeling, and other loopholes which would threaten consumers. But I look forward to hearing more about this proposal at today's hearing.

OPENING STATEMENT OF SENATOR JOHN KERRY

Thank you, Mr. Chairman. I would like to make just a few brief comments about the issue of drug exports facing this committee today. Over the years, the U.S. pharmaceutical industry has served the American people well by contributing significantly to their health and well-being. For this reason, if no other, it is prudent to examine and attempt to rectify those policies which may adversely affect the beneficial aspects of this important industry.

In our eagerness to do this however, we must be careful not to defeat the very purpose we seek: enhancing the overall public welfare. If our efforts lead to unnecessary risks diminution of the high regard in which our American industry is now held, then we benefit no one. As I see it, we face the difficult and delicate task of balancing our respect for the autonomy of other nations to make their own risk-benefit evaluations against our own deeply rooted concerns about health and safety.

Given the complexity of the challenge, I believe it is important for us to articulate and keep clearly in mind our policy objectives in considering this issue. Last year, Allan Fox and Nicholas Allard presented such objectives in the Food Drug Cosmetic Law Journal. I believe their points were well-expressed and would like to paraphrase them. Above all, any policy governing drug exports should be in the interest of promoting health and safety. Other objectives should result in stimulating innovation, promoting better relations between the United States and other nations, enhancing the effectiveness of our regulatory apparatus, and making U.S. industry more competitive in world markets.

Satisfying all of these goals will not be easy. It is my view that any ultimate revision of policy regarding drug exports will have to contain carefully constructed provisions and safeguards to insure that these objectives are adequately met.

The **CHAIRMAN**. This morning we will hear from four panels of witnesses who represent I think a very broad and, I might add, a varied range of views and provide a wide scope of expertise in the area of drug policy and legislation.

The first witness will be Dr. Frank Young, Commissioner of the Food and Drug Administration.

Dr. Young, it is always a pleasure to have the opportunity to hear your testimony and, of course, to work with you on legislative matters.

I understand that your testimony will reflect the administration's views on drug export reform. I want to thank you and your associates for being here today. We would like you to introduce your associates and we will be pleased to take your testimony at this time.

STATEMENT OF DR. FRANK E. YOUNG, COMMISSIONER, FOOD AND DRUG ADMINISTRATION, ACCOMPANIED BY DR. STUART NIGHTINGALE, ASSOCIATE COMMISSIONER FOR HEALTH AFFAIRS; AND THOMAS SCARLETT, GENERAL COUNSEL

Dr. Young. Thank you very much, Mr. Chairman. I would like to introduce on my right Dr. Stuart Nightingale, who is Associate Commissioner for Health Affairs, and on my left Mr. Thomas Scarlett, who is General Counsel.

We particularly welcome the opportunity to be part of this hearing and compliment you and the committee on the sustained interest in this very important legislation.

It is important to note that there are a number of considerations, and I will introduce if I may, please, my statement for the record and to save time would like to highlight some of these points.

The Chairman. Without objection, we will place all statements today in the record as though fully delivered, and we do appreciate summaries because we are all pressed for time.

Dr. Young. Thank you.

It is important to emphasize that the United States, in maintaining restrictive export requirements, is in sharp contrast to the other major drug producing countries. I have had the recent opportunity to visit with some of the individuals involved in exports from other countries and can personally attest to our increased restrictive nature. It is therefore appropriate to amend the U.S. laws and regulations so that practices which are prevalent in most other developed countries would also be possible here, thereby assuring that the American industry not continue to be unnecessarily disadvantaged and to allow the results of U.S. research to benefit foreign populations, some of which suffer from diseases not yet endemic in our own country.

We believe that there are three fundamental principles shown on the graph to my left that deal with the development of such testimony (appendix I). The first is the respect of the sovereignty of nations throughout the world. In this fashion, it is important to note that, as in your opening statement, the United States is more restrictive than other nations in export policy and by its very practice does not allow some of the nations throughout the world to devise their own programs for the import of biologicals and drugs.

The second important principle is the development of safety standards for the products. We believe that this has been possible in the past through FDA regulations and that programs can be devised to insure safety in the future as well.

A third important principle is the development of information sharing. In my testimony I have outlined a number of methods by which FDA has worked with the American Medical Association, the World Health Organization, and other agencies throughout the world to insure the orderly spread of information.

I would also like to focus on another point that is critical to this testimony: Namely, there are a number of diseases, primarily tropical diseases, throughout the world for which there is no effective medicine at this time. Many of these will be treated in the not too distant future we hope with the products of biotechnology. Diseases such as malaria affect 90 million people throughout the globe; trypanosomiasis, a very important problem, 65 million; and the list goes on from the diseases that we have been able to garner information from the World Health Organization (appendix II).

I personally feel as an individual who has been involved in biotechnology and an attender of the Asilomar Conference and a member of the first Recombinant DNA Advisory Committee, I believe that these parasitic diseases may well be attacked through recombinant DNA technology, and it is important that during the early development of this technology that we have the possibility of not only exporting these important products but stimulating research in the United States.

It is our opinion that the restrictive clauses that are in place may blunt some of the research activities, particularly in parasitic diseases.

Finally, I would point out that again as a scientist and a physician, I have been impressed, Mr. Chairman——

Senator KENNEDY. Excuse me. At this point, are the industries doing research in these areas which could make some impact on these Third World——

Dr. YOUNG. Yes, Senator Kennedy. One of the most exciting events that has occurred in recombinant DNA technology is the cloning of some of the antigens in regards to malaria, and there is some work in experimental model systems on vaccines for malaria. There are also drugs that are under investigation or have been approved in one instance for some of these diseases.

Senator KENNEDY. If I could ask, you might be able to supply that for the record.

Dr. YOUNG. I would be happy to supply that for the record and any other information in regards to technical points that you would like on biotechnology in relation to the field of parasitology.

The final point, Senator, follows right along on that, and that is that as a person involved in cloning, I have been impressed with the need for the export of products, rather than the very cutting edge of technology. If we had in the field of biotechnology the requirement to export our vectors that we have spent such a long time in perfecting the vehicles to other countries for the production of material, there would be a very substantial technological drain. I think our regulations in this way do foster this type of technological drain and again, as a person who has been extensively involved in biotechnology, I believe that some of the language that was developed in the previous years by Senator Hatch and Senator Kennedy, in your open statements, recognizes this principle. We at FDA would be very interested in helping you in any way that we can in supporting this legislation.

[The prepared statement of Dr. Young with information referred to in the text follow:]

PREPARED STATEMENT OF FRANK E. YOUNG, M.D., PH.D.

Mr. Chairman:

I am pleased to have this opportunity to discuss before your Committee our views on amending current law to authorize the export of new drugs and biologicals not yet approved in the United States to countries that have approved them. As you know, last year we testified at hearings on this subject before your Committee on June 28, as well as before the House Subcommittee on Health and the Environment on July 27.

As we stated last year, we strongly support such legislation. The United States is the only major developed nation with such restrictive export controls, and we believe there are important medical uses in foreign countries for many drugs not commercially available here. It is our view that the major principle to be observed in the consideration of legislation is: each sovereign government has the chief responsibility for determining the types of drugs that can be imported from abroad. Accordingly, the United States Congress has charged the FDA with the task of carefully reviewing drug products which can be sold to the public. Likewise, we believe it is primarily the responsibility of our trading partners to choose the types of drugs that are needed to effectively combat the health problems of their citizens. At the same time, we believe that certain key public health safeguards are essential, and I will describe for you several of them which we urge your Committee to consider in drafting new legislation.

Background

As the Committee recognizes, under the Federal Food, Drug, and Cosmetic (FDC) Act and its regulations, export of new human and new animal drugs is not now permitted for commercial use except for those drugs which have already been approved by the Food and Drug Administration (FDA) for use in the United States and antibiotics. Similar provisions of the Public Health Service Act govern the export of human biologicals.

In this regard, the United States, by maintaining such restrictive export requirements, is in sharp contrast to other major drug producing countries in the world where such exports are permissable subject to certain requirements. For example, in Canada, for drugs that are not approved in Canada, regulations specify that the package must be labeled for export and a certificate is issued stating that the package and its contents do not contravene any known requirement to the law of the country to which it is or is about to be consigned. In the United Kingdom, certificates are issued which indicate that the product being exported meets certain manufacturing standards which have been set by the World Health Organization (WHO). In Japan, the export of pharmaceuticals is governed by the "Export Inspection Law." Specifically, if a drug is not approved in Japan, it can be exported if it is approved for marketing by that foreign country which will import the drug. If a drug is to be approved for export use only, it is the responsibility of the importing country to assure that the products are safe and effective and the Japanese exporter must submit an application which includes a contract by the foreign importer that wishes the drug. The application must also include a listing of active and inactive ingredients, indications for use, and the form of the drug.

It is, therefore, appropriate to amend United States laws and regulations so that practices which are prevalent in most other developed countries would also be possible here, thereby insuring that American industry not continue to be unnecessarily disadvantaged and to allow the results of U.S. research to benefit foreign populations, some of which suffer from diseases not endemic to our country.

The fundamental principle underlying most countries' export laws is the sovereign right of individual countries to assess their own public health needs and to make their own decisions with regard to the products which should be available to them in order to meet their specific needs. As stated earlier, we agree with this underlying principle. We also feel there are two additional principles which are appropriate to govern our actions in this area: (1) the possibility of safety problems; and (2) the dissemination of available information that would enable countries to make informed judgments relative to these products. We believe that we have an obligation to prevent or suspend the export of any products which we have reason to believe may be hazardous to patients. In this context, we would also note that it is our belief that American drug companies will act responsibly in this area. We are not aware of any motivation sufficient to induce firms to knowingly ship unsafe products abroad. We also consider it essential that complete, unbiased drug information be available to foreign health authorities so they can make a proper determination on whether or not specific products should be imported.

Dr. John Dunne, who is Chief of the Pharmaceuticals Unit of the World Health Organization and whose views on international drug issues are highly regarded, also stressed these views in testimony before your Committee last year. He discussed the right of individual countries to make their own determinations regarding the drugs they need based on prevalent diseases and existent medical care. He further stated that "developed countries rigorously defend their national prerogative to control the availability and labeling of medicines marketed under their aegis."

Dr. Dunne also emphasized the need for sharing important drug information and described in some detail WHO's efforts to develop programs aimed at assuring an adequate flow of information on the quality, safety and efficacy of drugs in international commerce. I will address these international efforts later in my testimony.

It is also important to emphasize the positive medical value of a number of drug products that are approved in foreign countries but not in the United States. There are several reasons for this:

- Because of particular diseases and patient populations or cultural differences, some drugs are unique to conditions in specific countries other than the United States. Advances in biotechnology are facilitating the development of vaccines and diagnostic tests against infectious and parasitic diseases such as schistosomiasis, trypanosomiasis, brucellosis and cholera, which are not major health problems in this country but which pose significant world health problems.

  For another example, a vaccine for malaria would be of little use here, but there are areas of the world where malaria is a significant health problem and a vaccine is much needed. In 1982, it was estimated that the number of clinical malaria cases in the world was of the order of 90 million.

- There are instances where some drugs simply never get approved here. Applications are never even submitted to us because certain diseases are not prevalent here and, therefore, we do not need these products. For example, nine drugs on WHO's list of essential drugs are not approved in the United States and, therefore, are not available through American manufacturers in this country. Some of these drugs are vitally important in certain parts of the world but are of no relevance to the health of Americans. For example, Melarsoprol and Nifurtimox are used in the treatment of African trypanosomiasis (sleeping sickness). An estimated 45 million people are at risk of infection in Africa and much of the Sahara. Another example is sodium stibogluconate for the treatment of leishmaniasis. According to recent conservative estimates, the present global incidence of new infections may be on the order of 400,000 a year.

Although these products are not a high priority in the United States, incentives to develop such products may be enhanced if U.S. companies know that export to countries where a need for these drugs exists would be permitted.

- New Drug Applications may not be submitted for some products because the products are duplicative of those that are already available here, and would, thus, offer no real clinical advantages in the United States. These products would still be legitimately used in medical practice in foreign countries, and therefore the overseas market for these drugs might be considerable.

International Information-Sharing Efforts

As I stated earlier, the sharing of information is crucial if we are to maintain adequate safeguards for the use of these products. We therefore support, and would continue to support, international efforts to assure that all nations have access to information to assist in making risk/benefit determinations in the context of their own health needs, the diseases and health-related characteristics of their populations, the nature of their health care delivery systems, and the availability of treatment alternatives. We will also continue our important bilateral efforts, which include periodic mailings to foreign drug regulatory authorities of information on new regulations and guidelines, as well as information on drug approvals and withdrawals and concerns we may have regarding the safety or efficacy of specific drugs.

A current example of our efforts to strengthen foreign national drug regulatory authorities' decisionmaking abilities includes collaboration with the American Medical Association which resulted in making available copies of their book, "AMA Drug Evaluations" worldwide. FDA collaborated with the AMA in this activity because of our view that it is important to have authoritative, objective, and current information available to regulatory authorities and clinicians all over the world. Our collaborative efforts are based on, but not limited to, official FDA drug labeling, current literature, unpublished materials provided by investigators, and commentaries by eminent authorities. We also encouraged the worldwide dissemination of the *Physicians' Desk Reference* (PDR) by the Pharmaceutical Manufacturers Association to drug regulatory authorities worldwide. The PDR is a compilation of official FDA labeling and is of great importance to drug regulatory authorities. We are pleased to note that the distribution of this important reference has been completed.

The United States has actively participated in discussions concerning the WHO Certification Scheme for Pharmaceuticals Moving in International Commerce. This system, adopted by WHO in 1975 and currently agreed to by over 100 countries, including the United States, permits an importing country to obtain from the government of an exporting country current information on the quality and status of a drug in the country of export regardless of whether or not it is approved for marketing in the country of origin.

The United States is also involved in other international activities for ensuring the flow of information on the safety and efficacy of pharmaceutical products. These activities include regular submissions of information as well as notifications of significant regulatory actions on drugs to the WHO for subsequent dissemination in WHO's regular publications, _Drug Information Circulars_ and _WHO Drug Information Bulletins_. The United States also serves as a National Collaborating Center for the WHO International Drug Monitoring Scheme, a system coordinated by WHO for collecting and reviewing adverse drug reaction reports that occur worldwide. In addition, the United States participates in the biennial International Conferences of Drug Regulatory Authorities, which provide a forum for the direct exchange of drug information and discussions of regulatory actions. The first such conference was hosted by the United States in Annapolis, Maryland in 1980, the second conference was held in Rome, Italy in 1982, the third, last year in Sweden and the next is planned for Japan in 1986.

With regard to animal drugs, the United States was instrumental in organizing the International Consultation on Veterinary Products Registration cosponsored by WHO. This group met in 1982 and 1984 to, among other things, assure the flow of information on the safety and efficacy of animal drugs.

Incidentally, there are also upcoming conferences which will address issues relative to foods and medical devices. Specifically, a Food Conference cosponsored by the Pan American Health Organization and the Food and Agriculture Organization of the United Nations is to be held in Washington, D.C. in August 1985. The FDA and the U.S. Department of Agriculture are also cosponsors. In June 1986, the International Conference of Medical Device Regulatory Authorities, cosponsored by the FDA and WHO will convene in Washington, D.C. All WHO member states will be invited to attend.

FDA also participates in providing training and technical assistance, both under bilateral agreements and under the auspices of the WHO Action Program on Essential Drugs, particularly to less developed countries, to enable them to develop national policies and regulatory systems for assuring that safe and effective drugs of high quality are available to their people. For example, within the last three years, FDA personnel have served as consultants in various regulatory and technical areas, especially drug quality procedures in a number of developing countries including Nigeria, Indonesia, Peoples Republic of China, Guatemala, and Egypt to name a few. In fact, this week we are providing expert consultants to the Western Pacific Region of WHO to assist WHO in holding a regional conference on pharmaceuticals. Also, during the past year, over 100 foreign officials and scientists visited FDA for consultations and training in methods for assessing the safety and effectiveness of marketed drugs.

We believe that this considerable effort by WHO, as well as our own efforts in cooperation with WHO, to desseminate vital drug information and to provide technical training and assistance provides health care professionals and government authorities with valuable and up-to-date information to make informed judgments and, therefore, to help maintain adequate safeguards to protect the public health of their citizens. At the same time, the governments of other nations would be permitted to exercise their own risk/benefit decisions with respect to the pharmaceuticals they believe are suitable for use in their countries, thereby maintaining respect for national sovereignty.

Dr. Dunne expressed similar views last year in offering his support for your legislation by emphasizing that channels of communication between national drug regulatory authorities have improved considerably in recent years, allowing even the smallest of these authorities to assume its responsibility to select drugs for distribution in their countries by facilitating the flow of important information on the safety and efficacy of drug products.

I recently discussed these issues with Dr. Dunne in Geneva. He confirmed his continuing view that drugs that are not yet approved could be exported with safeguards analogous to those imposed by other leading developed nations in WHO.

I would make one last comment here. While we would not want to be in a position of withholding potentially useful drugs from the marketplace in countries where they may be beneficial, we are sensitive to the need to avoid the inappropriate export of drugs which may pose serious safety problems. If new legislation is enacted, we will make every effort to avoid this.

Conclusion

In conclusion, Mr. Chairman, I reemphasize that we strongly support your efforts in behalf of this type of legislation. We believe that appropriate safeguards, together with the other efforts we described would provide an adequate measure of control over the export of new human and animal drugs and human biologicals not approved in the United States. We remain available to the Committee to provide technical assistance to develop legislation regarding the export of such products which may be of benefit in other countries.

That concludes my prepared statement, Mr. Chairman. I will be glad to answer any questions you may have.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

The Honorable Orrin G. Hatch
Chairman, Committee on Labor
  and Human Resources
United States Senate
Washington, D.C. 20510

Dear Mr. Chairman:

As requested by your staff, I have reviewed the transcript from the hearing before your Committee on June 6 on the issue of amending current law to authorize the export of unapproved new drugs and biologicals and would like to clarify for the record two issues which came up during our discussion.

First, on page 22 of the transcript, you asked me to comment on the two versions which have been considered as possible approaches to allow for such exports. As I said during our discussion, because so many countries now have increased regulatory capabilities, a list could be developed of those countries that have their own regulatory standards. Export could then be permitted to those countries.

However, in considering any new legislation, I believe it is most important to provide a mechanism whereby drugs could also be exported to developing countries. Certain specific diseases are prevalent in these countries which are not major health problems in the United States (or, for that matter, in other more developed countries), but which pose significant health problems where they occur. Drugs to treat these diseases are vitally important, and it would seem appropriate to allow these drugs to be exported to countries where they would be beneficial. My prepared statement addresses this point in more detail.

In addition, in those instances in which a drug is intended to treat a condition not prevalent in the United States so that submission of an NDA to allow domestic use is unlikely, an alternative mechanism to the IND/NDA procedures might be for the establishment of a drug Master File for a product intended for export as a means for the FDA to receive relevant existing information concerning the drug's composition, labeling, history of use, and evidence of safety and effectiveness.

Second, on page 24, you asked about the advisability of requiring that the unapproved product being offered for export be the subject of an IND in order to be exported to a listed country. As has been mentioned previously, the countries which would be listed in the legislation would be those that have in place regulatory mechanisms governing the availability of drugs. The existence of an IND in the United States may not offer any significant advantage in this instance.

However, with regard to countries without such regulatory mechanisms, should it be determined by Congress that any condition be set for export then, even though the different phases of drug testing are difficult to separate out, the fact that preliminary human testing has been conducted under an IND provides at least some information regarding the appropriateness of considering further use of the drug in humans. Although the amount of information available under an IND is limited, and one would not want to base a foreign marketing decision on an IND alone, the existence of a U.S. IND does provide some additional evidence of a drug's safety which, together with other appropriate safeguards, would help determine the appropriateness of exporting the drug to such countries.

I appreciate the opportunity to discuss this important issue with you. If I can be of any further assistance, please contact me.

Sincerely yours,

Frank E. Young

Frank E. Young, M.D., Ph.D.
Commissioner of Food and Drugs

APPENDIX I

PRINCIPLES

1. Sovereignty of Nations
2. Safety of Products
3. Information — Sharing

DISEASE INCIDENCE WORLDWIDE

MALARIA
90 Million

TRYPANOSOMIASIS
(Sleeping Sickness)
65 Million

SCHISTOSOMIASIS
200 Million

FILARIASIS
90 Million

ONCHOCERCIASIS
20-40 Million

LEISHMANIASES
New Infections
400,000 Per Year

LEPROSY
10-11 Million

Data Source: World Health Organization

Excerpts from:

A similar method involves using mutation/selection procedures on pathogenic bacteria to select bacteria that die after a short period of time in the body. For instance, a mutant of the typhoid-causing bacterium, *Salmonella typhi*, type Ty-21a, accumulates toxic amounts of galactose during growth and causes its own death. This mutant can proliferate within the body for a short time, and its presence elicits an immune response that protects against the disease. The Swiss Serum and Vaccine Institute, in association with the French Institut Pasteur, has developed an oral typhoid vaccine of this type.

Other workers have taken this typhoid vaccine strain and incorporated a plasmid with a gene encoding a protein normally produced by *Shigella sonnei*, one of the bacteria which cause dysentery. In mice, this "hybrid" strain elicits immune responses that protect against both the dysentery and typhoid organisms. Thus, it may be possible to construct a multipurpose oral, attenuated typhoid-dysentery vaccine organism that will produce "protective" antigens for both dysentery and typhoid (51).

Parasitic disease vaccines

Diseases caused by parasites, including protozoa, pose major barriers to acceptable health standards for millions of people throughout the world (see table 25). Many of these organisms exhibit even more extraordinary degrees of complexity than bacteria, however, and lack of basic knowledge restrains new vaccine development in virtually all cases (51). As basic knowledge accrues, immunization against diseases caused by parasites may eventually be the greatest breakthrough in health care provided by biotechnology.[*]

Table 25.—Estimated Worldwide Populations Affected by Parasitic Diseases in 1971

Type of parasite	Diseased population (in millions)
Intestinal parasites:	
Ascariasis	650
Ancyclostomiasis	450
Amoebiasis	350
Trichuriasis	350
Periocular parasites:	
Trachoma	Greater than 400
Systemic parasites:	
Filariasis	250
Schistosomiasis	180
Malaria	100
Leishmaniasis	N.A.[a]
Trypanosomiasis	7

[a] N.A. = information not available.

SOURCE: Office of Technology Assessment, based on data from World Health Organization, *Report for the Special Programme for Research and Training in Tropical Diseases*, Geneva, 1976.

Progress in developing malaria vaccines exemplify efforts to realize biotechnology's potential in combating parasitic diseases. Because of the lack of a vaccine, combined with parasitic resistance to the drugs used in malaria control (e.g., chloroquine), malaria remains the most prevalent infectious disease in the world.[**] Historically, the search for malaria vaccines has been hampered by difficulties in growing the malarial parasite *Plasmodium* (which is transmitted by female *Anopheles* mosquitoes) in the laboratory. Other difficulties stem from *Plasmodium's* complex lifecycle and the apparent ability of the parasite to evade the body's immune system. In addition, vaccines based on killed, injected whole *Plasmodia* presently require the use of powerful adjuvants (additional components of vaccines that boost immune responses) in test animals which are too strong for human use.

The complexity of *Plasmodium's* lifecycle hints at the difficulties in developing a vaccine that protects against all forms of malaria. As shown in figure 14, the sporozoites, injected into the blood

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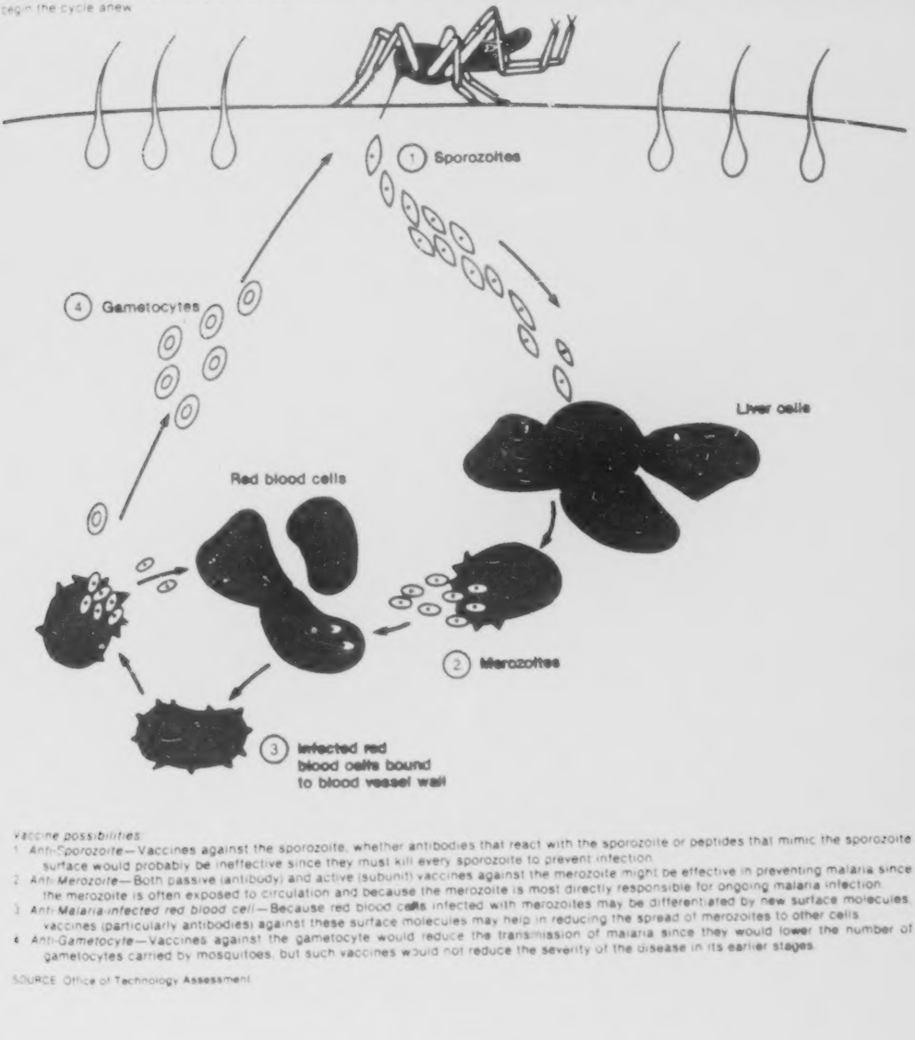
[*] The U.S. National Academy of Sciences and the Agency for International Development convened meetings in July and December 1982 on the applications of biotechnology most significant for the developing world. Recommendations were made with respect to research priorities on the basis of applicability of the new technologies and other considerations (88,145). The only human parasitic diseases that ranked among the top priorities for development at this time were leishmaniasis and malaria. Leishmaniasis is a family of diseases, caused by sandfly-transmitted protozoa, which is considered to have grossly underestimated public health importance in South America, Africa, and the Middle East. It was identified for special attention because there is evidence that immunity can be developed by people in sandfly-infested areas over a period of time. An understanding of this immunity may provide ways to prevent leishmaniasis.

[**] There are now an estimated 300 million malaria cases per year and a very high mortality rate for children (1 million deaths in Africa alone per year) (158). About 850 million people live in areas where malaria continues to be transmitted despite activities to control it. An additional 345 million people reside in areas with little or no active malaria control efforts. Over half of the health budget of India is spent on malaria control. Resistance to both drugs and insecticides and the number of new malaria cases are all increasing at alarming rates (155). No vaccine is currently available.

Figure 14.—The Lifecycle of *Plasmodium*, the Malarial Organism: Possibilities for Development of Vaccines for Malaria

The malarial infection begins when a person is bitten by an *Anopheles* mosquito that bears *Plasmodia*. Sporozoites (1) are injected into the bloodstream, where they may remain for only 30 minutes before they infect liver cells. Within the liver cells, each sporozoite divides into six to twenty-four merozoites, the next *Palsmodium* life-stage. Merozoites burst from the infected liver cell (2) destroying it, and enter the blood stream, where they infect red blood cells and proliferate. In subsequent waves of infection, merozoites burst from the red blood cells and spread to other red blood cells. Red blood cells infected with merozoites may produce new cell surface molecules which allow them to bind to blood vessel walls (3). Some of the merozoites go on to become gametophytes, the next life stage (4). These gametophytes are picked up by another *Anopheles* mosquito in another bite; they reproduce within the mosquito and form sporozoites, which may be injected into another person to begin the cycle anew.



Vaccine possibilities:

1. *Anti-Sporozoite*—Vaccines against the sporozoite, whether antibodies that react with the sporozoite or peptides that mimic the sporozoite surface would probably be ineffective since they must kill every sporozoite to prevent infection.
2. *Anti-Merozoite*—Both passive (antibody) and active (subunit) vaccines against the merozoite might be effective in preventing malaria since the merozoite is often exposed to circulation and because the merozoite is most directly responsible for ongoing malaria infection.
3. *Anti-Malaria-infected red blood cell*—Because red blood cells infected with merozoites may be differentiated by new surface molecules, vaccines (particularly antibodies) against these surface molecules may help in reducing the spread of merozoites to other cells.
4. *Anti-Gametocyte*—Vaccines against the gametocyte would reduce the transmission of malaria since they would lower the number of gametocytes carried by mosquitoes, but such vaccines would not reduce the severity of the disease in its earlier stages.

SOURCE: Office of Technology Assessment.

stream during the mosquito bite, infect liver cells to initiate infection. Large numbers of merozoites, the next life-stage, proliferate within the liver cells and, bursting into the blood stream, successively infect large numbers of red blood cells. Some of the merozoites remain blood-borne; other merozoites develop into gametocytes, which are picked up by mosquitoes, reproduce to form new sporozoites, and begin the cycle anew. Additionally, *Plasmodium* has the ability to evade the immune system over time.

Since the pathology of malaria is caused largely by *Plasmodia* in the merozoite stage, the merozoite appears to be the best target for vaccines. Even one sporozoite reaching a liver cell is capable of causing malaria, so vaccines against this stage must kill every sporozoite to be effective. The gametocyte itself is not pathogenic; an antigametocyte vaccine, therefore, would serve only to reduce the transmission of the disease.

Many investigators (particularly in the United States, the United Kingdom, and Switzerland) are developing MAbs that may be useful in malaria research (153). Antisporozoite and antimerozoite MAbs that inhibit the in vitro multiplication of *Plasmodia* and antigametocyte MAbs that inactivate male gametes have been developed (153). Also, MAbs that destroy merozoite-infected red blood cells have been developed. Such MAbs may prove useful as vaccines that confer passive immunity (19,87,160).

The most promising use of such MAbs is in the isolation of surface antigens which might be used for the development of subunit malarial vaccines. Though quantities of surface antigens obtained by MAb precipitation are too small for use as vaccines, these purified antigens provide a starting point for developing other MAbs with an even greater affinity for *Plasmodium* for use as passive vaccines. They may also provide a starting point for using rDNA technology to isolate large amounts of antigen. Workers at New York University (NYU) recently reported the successful cloning and expression in *E. coli* of a surface antigen from the sporozoite stage of one species of *Plasmodium* using rDNA technology (28), and similar efforts to obtain quantities of antigen from other *Plasmodium* species and life stages using rDNA technology are underway (54). These rDNA-produced surface antigens may serve as protective malarial vaccines.

NYU's "antisporozoite vaccine" has been the subject of a widely publicized dispute between NYU; Genentech (U.S.) (the proposed manufacturer of the vaccine); and the World Health Organization (WHO) (which, with the U.S. Agency for International Development, sponsored NYU's basic research with the standard provision that all WHO-funded work must be "publicly accessible").[*] When it became clear that Genentech would not obtain an exclusive license to commercialize the vaccine, the company bowed out of negotiations. At present, no other arrangements to pursue large-scale rDNA production of the sporozoite antigen have been made.

As mentioned earlier, a vaccine effective against only the sporozoite stage of a single *Plasmodium* species may not prove to be fully protective against malaria. Ultimately, malaria vaccines may include a variety of stage-specific antigens that result in combined sporozoite and merozoite neutralization, accelerated removal of infected red blood cells, and prevention of gametocyte transmission to the mosquito (158). The delay of further development of NYU's potential milestone sporozoite vaccine imposed by the turmoil over commercialization, however, has raised concern that, in the future, profit motivations may delay the development of urgently needed pharmaceutical products made possible by biotechnology (75,90). Despite their promise, the development of effective malarial vaccines appears to be several years away.

For a variety of reasons, biotechnology holds less promise for vaccine solutions for other parasitic diseases than for malaria. For most of the parasites, there are formidable problems related to culture of the pathogenic organisms and establishment of meaningful models of the human disease in animals. For example, the parasite that causes schistosomiasis, a disease that ranks second only to malaria as a cause of morbidity and mortality from parasitic organisms, is difficult to culture in the laboratory. The ability of this parasite to alter its susceptibility to host immunological responses and the difficulty in obtaining sufficient quantities of an antigen have hampered efforts to develop a vaccine for schistosomiasis.

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[*] A similar situation arose with regard to the cloning of several more malarial surface antigens at Walter and Eliza Hall Institute of Medical Research in Australia. This research was also partially funded by WHO (110).

Much basic research on parasites is needed in order to develop effective antiparasite vaccines using rDNA technology. The techniques of biotechnology have accelerated the study of parasitic diseases, but urgently needed pharmaceutical applications in this area are still in early stages.

Antibiotics

For the past three decades, antimicrobial agents for the treatment of infectious diseases caused by bacteria have consistently led worldwide sales of prescription pharmaceuticals. Novel antibiotics, produced mainly by traditional microbial bioprocesses, continue to be developed and introduced each year (especially in Japan in recent years). Methods of biotechnology such as the following offer strong innovative possibilities for producing new antibiotics:

- *"Sexual" recombination.* A technique known as protoplast fusion, whereby the contents of two micro-organisms are fused to give one cell, enables researchers to induce rapid improvements in bacterial germplasms. Protoplast fusion allows the rejuvenation of strains of industrial microbes that have lost vigor as a result of mutation and selection procedures that have been performed to increase their antibiotic productivity. The fusion of micro-organisms is beginning to yield new (hybrid) antibiotics (22).*
- *Recombinant DNA technology.* Gene coding for enzymes and other metabolic proteins can be cloned into antibiotic-producing micro-organisms to add steps to existing biosynthetic pathways that improve products or manufacturing processes. Ongoing research includes: 1) the rDNA-mediated transfer of acyltransferase genes among species of bacteria to obtain solvent-extractable cephalosporins (149); 2) the combination of genes via rDNA technology and transformation to obtain direct, efficient synthesis of the antibiotic amikacin (149); and 3) Eli Lilly's utilization of rDNA technology to improve the production of the antibiotic tylosin (4).

The combination of new and traditional technology in the pharmaceutical industry holds tremendous potential for improvement of micro-organisms used in antibiotic production and the isolation of new antibiotic products. Japanese pharmaceutical companies, with their extensive bioprocessing resources, are placing great emphasis on new antibiotic research (114). This emphasis may be due to the fact that antibiotics comprise 25 percent of (1981) ethical drug sales in Japan (compared to about 8 percent in the United States) and that at least 28 percent of the antibiotic sales in Japan now arise from antibiotics produced in the United States (120,125).

Monoclonal antibodies

MAb technology currently leads other forms of biotechnology in commercial use, as measured by numbers of products on the market. Its lead is largely due to MAb in vitro diagnostic products. In vitro diagnostic products do not have to undergo the same rigorous safety testing required of

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*Through protoplast fusion and selection, researchers at Bristol-Myers (U.S.) developed an improved method of producing purer penicillins that has accounted for 8 percent per year improvement in penicillin productivity over the past 4 years. Other genetic approaches produced 60 to 70 percent improvements in yields of cephalosporins (a class of antibiotics) in the same period. Genetic research by Pfizer, Inc., at laboratories in the United Kingdom and United States, have gradually lowered costs of producing oxytetracycline, a long established antibiotic, to costs similar to bulk chemical production, to give prices of several dollars per kilogram (73).

Excerpts from Human Fertility, Health and Food
(U.N. Fund for Population Activities)

THE PROMISE OF BIOTECHNOLOGY FOR PHARMACEUTICALS AND OTHER HEALTH CARE APPLICATIONS

Henry I. Miller[1]

Abstract

Advances in new biotechnology, especially the production of monoclonal antibodies and the manipulation of genes with recombinant DNA technology, have demonstrated its scientific and commercial viability. However, accurate predictions of biotechnology's contributions during the next decades are extremely difficult, for a number of reasons. These include: the question of what is actually ascribable solely to the new biotechnology (as opposed to incremental improvements in older technologies); and our inability to know the outcome of clinical trials of various new products. However, potential health care applications of the new biotechnology are discussed and, where possible, order-of-magnitude predictions are hazarded.

Introduction

As will be evident from even a cursory examination of this volume, advances in "biotechnology" are expected to exert impacts in various, widely diverse aspects of the human experience, affecting - perhaps profoundly - food supplies, health care and, necessarily, population growth.

What is biotechnology, this phenomenon that has spawned literally hundreds of new companies world-wide, with market capitalization in the tens of billions of dollars? What does biotechnology presage for science and society in general, and for the production of pharmaceuticals and other health care applications in particular, over the next decade or so? Even informed speculation of this kind is fraught with many hazards. The U.S. National Academy of Sciences has performed five- and ten-year prognostications since the mid-1930's; they have missed anticipating nuclear energy, microprocessors, and molecular biology, among other developments. However, such speculation can serve a useful purpose: it may enable us to predict order-of-magnitude effects, or at least to determine whether an effect will be closer to naught or to a googol plex.

First, let us define biotechnology as encompassing these processes: (a) use of microorganisms, plant cells, animal cells or parts of cells such as enzymes, to produce commercial quantities of useful substances; (b) construction of microorganisms, cells, plants or animals with useful traits by recombinant DNA techniques, cell fusion and other methods (but not including traditional genetic breeding techniques); and (c) the application of molecular biology to understanding how cells and organisms function in order that we can alter or repair their activities.

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[1] The author is a Medical Officer in the U.S. Food and Drug Administration's National Center for Drugs and Biologics. This article was written by him in his private capacity. No official support or endorsement by the Food and Drug Administration is intended or should be inferred.

It is unlikely that the current product pattern in the "bioprocess (i.e. the synthetic aspect of exploitive biotechnology, in which complete living cells or their elements [enzymes, receptors, etc.] are employed to effect desired physical or chemical changes) industry" will change radically over the next two decades. That is, the production of high unit-value products directed toward specialty markets, primarily pharmaceutical, will continue. There will also be additional commercial enzyme products, but these too will be aimed at special, rather than broad, applications.

A problematical aspect of estimating the future markets for bioprocessing for biotechnology in general, is that these markets will be of two kinds: (a) those that are created by completely novel products (or by the new technology providing markedly increased availability of products), and hence, not detracting substantially from pre-existing markets; and (b) those that employ new techniques to manufacture old products, causing a shift from old to new markets, or perhaps, expansion of old markets as the costs of production are reduced. Examples of the first situation would be the newly created markets for therapeutics derived from hybridoma-produced monoclonal antibodies or for recombinant DNA-derived human growth hormone. The second situation would be exemplified by the shift from the traditional animal insulins (obtained from bovine and porcine pancreas) to recombinant DNA-derived human insulin obtained from bacteria, or by the production of amino acids via newer bioprocesses.

Antimicrobials as a Paradigm of the Difficulty of Defining a Market

The dilemma of what to include in prognostications of the future markets for biotechnology can be dramatic; the example of antimicrobial agents is illustrative. Antimicrobial agents for the treatment of infectious diseases have been the largest selling prescription pharmaceuticals in the world for the past three decades. Most of these agents are antibiotics — antimicrobials — naturally produced by microorganisms rather than by chemical synthesis or by isolation from higher organisms. The field of antibiotics, in fact, provides most of the precedent for employing microbial fermentation to produce medically-applicable substances. The U.S. has been prominent in their development, production and marketing, with the result that American companies account for about half of the roughly $3 billion worth of antibiotics sold in the free world annually.

Antibiotics are complex, usually nonprotein, secondary metabolic substances which are generally the end products of a series of biological steps. While knowledge of molecular details in metabolism has made some difference, not a single antibiotic has had its complete biosynthetic pathway elucidated. This is partly because there is no single gene that can be isolated to produce an antibiotic. Significantly, however, mutations can be induced within the original microorganism to increase the level of production. Indeed, one of the major applications of recombinant DNA technology is expected to be the improvement of pre-existing strains of commercially important microorganisms. This has already been achieved in some industrial laboratories.

If one accepts that a major by-product of recombinant DNA technology (in addition, that is, to the much publicized production of human interferons, insulin, and so forth) is likely to be this small but important incremental improvement, the problem then becomes — for the purposes of prediction or evaluation — how to define new biotechnology's incremental contribution. If, for example, recombinant DNA techniques were widely used to induce the microorganisms producing tetracycline (a $1 billion/year market) to increase their output a few percent, would one be justified in adding $1 billion to new biotechnology's tally? While this kind of reasoning is misleading, it seems to be the basis for many of the hyperbolic estimates of the markets likely to be ascribable to the new biotechnology.

Markets for the Human Applications of Biotechnology — Present and Future.

With the lessons of the preceding section in mind, the estimates here will attempt to include both the total amounts as well as increments resulting from the new technology.

Human Pharmaceuticals

The use of hybridomas to produce monoclonal antibodies has been, and continues to be, one of the fastest developing areas of biotechnology. Clinical diagnostic kits containing monoclonal antibodies are already commercially available, and the 1983 total market is likely to be in the tens of millions of dollars, all of this representing an increment ascribable to the new technology. In the future, monoclonal antibodies for passive immunization and neutralization of toxins are expected. Clinical trials using monoclonal antibodies for cancer therapy are in progress. Moreover, monoclonal antibodies could also be a powerful tool in separations of industrially important high value-added products. The total monoclonal antibody market should rise steadily during this decade, to perhaps several hundreds of millions.

Despite the continuing hyperbole in the media about the imminent contributions of recombinant DNA in human therapeutics, there is relatively little expected to be marketed by the end of the decade, especially if one considers incremental markets. Human insulin produced by recombinant DNA techniques was approved for marketing by the U.S. Food and Drug Administration in late 1982, earlier than most had predicted; however, the human insulin appears to be no better than conventionally produced porcine insulin. In any case, the human insulin market will not be a new one, but will simply represent a shift from the half-billion dollar annual animal insulin markets.

More significant will be the recombinant DNA-derived human interferons and human growth hormones, since these are likely to represent primarily new markets (limited availability has in the past severely restricted potential markets). Human interferons have been employed in the past only sparingly (because of limited pre-recombinant-DNA supplies) in clinical trials as anti-viral or anti-tumor agents. The market is currently $25-50 million but could grow perhaps ten-fold by the end of the decade, with virtually unlimited availability with production by recombinant DNA techniques if — a big if — clinical trials demonstrate clinical safety and efficacy.

Human growth hormone (hGH), currently purified from human cadaver pituitary glands, represents approximately a $75 million market. With virtually unlimited availability of the hormone now that recombinant DNA techniques are being employed, hGH will soon be tested for other conditions besides short stature of pituitary origin; these include accelerated wound, burn, and fracture healing. In any case, by the end of the decade it would not be surprising to see the market for hGH in the $150-200 million range, perhaps half of this representing an increment due to new biotechnology.

A new generation of thrombolytic agents could compete for the approximately $200 million world-wide market now held by urokinase and streptokinase; these include a tissue plasminogen activator (variously obtained from genetically-engineered microbes or from cell lines in tissue culture) and a pro-urokinase purified from kidney cells in tissue culture. Clinical trials have only just begun and it is premature to attempt predictions of safety or efficacy at this time. However, it should be noted that if these products are licensed for marketing and they are effective when administered by peripheral intravenous injection (as opposed, for example, to intra-coronary-arterial injection after myocardial infarction), the size of the market should increase substantially, especially in the U.S., where the currently approved thrombolytic agents are used only sparingly.

New biotechnology will probably make several contributions in the area of vaccines, creating markets that are largely new, for prophylaxis against such diseases as hepatitis B and genital herpes. While difficult to estimate accurately, such markets will, in all likelihood, be limited because of the probable one-time nature of administration of such vaccine preparations. The technology is even now capable of producing vaccines and other therapies for some of the great parasitic scourges of mankind that plague large parts of the developing world. Malaria and the trypanosome-caused diseases — sleeping sickness, Chagas' disease — are under investigation by molecular biologists and medical entomologists, and significant progress has already been achieved in the development of genetically engineered vaccines. However, in the absence of potent economic incentives (presumably provided by other than free-market forces), it is unlikely that these will soon be ready for clinical trials and licensing. The impetus for the development of such products could come from the military or from funding by governments, international organizations or philanthropies.

Other drugs in the biotechnology pipeline are likely to be economically insignificant for several reasons. These include: lack of interest by U.S. physicians (e.g. urokinase, vide supra); or limited application (somatostatin); or simply that resultant markets would represent merely a shift from the markets of conventionally-produced substances (e.g. human serum albumin, a plasma expander).

Food/Food Additives

New biotechnology is expected to make several contributions in this area for the production of enzymes used in food processing. These include glucose isomerase (used for converting glucose to high-fructose syrup) and rennin (cheese production). The current market size for these enzymes is approximately $40 million each. The increment in these markets as a result of the new biotechnology is not expected to be substantial.

Single-cell protein (SCP) consists of the dried cells of single-celled organisms such as yeast, bacteria or algae which, besides containing a large proportion of protein, also contains fats, carbohydrates and other substances.

SCP has been touted as a potential solution to protein shortages in food for humans and animals. However, at present the cost of producing SCP is high, and SCP is not currently competitive with soybeans or fishmeal as a protein supplement in the U.S. Genetic engineering would have to enhance the capability of the organisms to produce protein by an additional factor of five to ten (weight/volume) to make commercial production of SCP cost-effective in the U.S., and recombinant DNA techniques are currently being applied in hopes of making the process economically more advantageous. However, for countries with inadequate fertile land or unreliable climatic conditions, but possessing an inexpensive feedstock, SCP is even now of interest as a way to balance agricultural trade. Japan, England and several other European countries have built SCP plants in the last ten years, and South Africa seems likely to follow suit. A world leader in production of SCP is the USSR, interested in its potential to decrease Soviet dependency on foreign sources of feed protein.

Conclusions and Prognosis

New biotechnology has proved itself scientifically and commercially viable in the area of health care applications such as the production of pharmaceutical products. A number of diagnostic products utilizing hybridoma-derived monoclonal antibodies, as well as human insulin produced in bacteria manipulated with recombinant DNA techniques, are approved for marketing in the U.S. and elsewhere. Other drug and biological products, including human growth hormone, interferons, anti-viral vaccines, thrombolytic agents, and monoclonal antibody preparations are in clinical trials. Facilities for producing single-cell proteins from genetically-manipulated microorganisms exist in Western Europe, Japan and the Soviet Union, and are planned for South Africa. Revenues from such products are currently in the tens of millions of dollars and could well expand several orders of magnitude by the end of the century. While the technology exists for the development in this time frame of vaccines against some of the great scourges of mankind - for example, the parasitic diseases that ravage the developing world - it seems unlikely that there will be rapid progress in this area without support from forces other than those of the free market.

The **Chairman**. Thank you, Dr. Young.

Dr. Young, would you describe for us generally the risk benefit determination involved in approving a drug? Specifically, if a drug is approved here, does it mean that it is risk free or that it will never cause harm to those who use it elsewhere?

Dr. **Young**. Absolutely not, Senator. There is no drug that we could state is risk free. We constantly do risk-benefit analyses, and there is some degree of variation of populations to susceptibility to diseases and reaction to medicinals. This is why we feel very strongly that each country should be able to have an opportunity to exert its own sovereignty and meet its own Nation's medical needs.

The **Chairman**. Are there not occasions when the United States and other developed countries still find it necessary to revoke the approval of a drug already approved by the appropriate agency and already on the market? If that is so, why is it?

Dr. **Young**. After we go through a very extensive investigational new drug phase and then finally approve the new drug application for the marketing of the drug, we have still only seen that drug tested on approximately 3,000 to 5,000 people. When millions of individuals use a product, sometimes we find some minor side effects or some adverse reaction that could not be anticipated, and it is extremely important therefore that we have the ability, as we have exerted in the past, to remove drugs that are not appropriate.

The **Chairman**. In your statement, your written statement, you say "Channels of communication between national drug regulatory authorities have improved considerably in recent years." Could you be just a little more specific and describe for us, for the committee what you mean by that?

Dr. **Young**. We have had a number of meetings, many of which were catalyzed by the United States, for example, the tripartite meetings with Canada and Great Britain, and cosponsorship with WHO of meetings of regulatory officials.

For example, in the early eighties we sponsored, in cooperation with WHO, a conference of drug regulatory officials in the United States. As I have had a chance to meet with regulatory officials throughout the world, I am impressed with two things: First, the standards that FDA have adopted are by and large embraced in many nations; second, there has been a vast improvement in the ability of nations to enforce and develop their own regulations, to certify good laboratory and good manufacturing practices and, more critically, an understanding of the principles of safeguard of populations and a genuine desire to do so.

The **Chairman**. Now, Dr. Young, you are aware of the various approaches which are under consideration—one would provide a mechanism for export to developing countries and one would not. Could you give us your opinion regarding the desirability of either or both of these approaches?

Dr. **Young**. There are two major models that have been considered by this committee and other committees in the past. One model would be built upon recognizing the very point that we were just discussing, an increase in regulatory capability in developed countries around the world. In that format, one could establish a list of countries that would be most likely to have similar regulatory methodologies to that in the United States, for example, countries such as Israel, Federal Republic of Germany, Great Britain, Canada, Japan, and many nations of this sort which have under their own standards developed such regulatory methodologies.

It would be also important to consider, as I mentioned in the tropical disease cases, that there may be some particular compounds, vaccines, biologicals that could be developed tnat would be of unique capability in some of the other countries, and it might be appropriate to have methodology whereby such compounds could be exported as well during the approval process.

A second method would be to use the model developed by the device legislation. In that case, there is an export to the other country if the device is approved in that country, if the country requests it, and if FDA after review feels that there is an appropriate device to export. Even under such cases as you raised in your first question, it is possible for us to examine and, if necessary, revoke the capability of exporting a device. We believe the safeguards are there.

The CHAIRMAN. Is there any real virtue in requiring that a drug be subjected to an IND or an investigative new drug exemption at FDA before it can be exported to one of the listed developed countries?

Dr. YOUNG. That is a very difficult question. The important principle is to recognize that the IND is a difficult phase to divide into phase I, phase II, and phase III to and make an exact distinction. Therefore dividing and saying at one phase of an IND or another phase of an IND would be less appropriate.

The registration of a drug through an IND process would not be an inappropriate burden to consider.

The CHAIRMAN. If legislation is enacted requiring FDA to assess which foreign regulatory agencies are "adequate" to review the safety and efficacy of drugs, how would FDA go about establishing criteria and procedures to handle this particular duty?

Dr. YOUNG. We would need advice, Mr. Chairman, from the Congress as to the principles that we would use. It is difficult but not impossible for us to sit in judgment on other regulatory agencies throughout the world. However, we would be prepared to look at criteria in relation to the type of approval processes that are extant outside the United States. Hopefully, you would provide guidance in the first list that could be developed and we would be able to deal with subsequent additions and deletions to that. The principles though would be based on regulatory standards, and the ability to monitor safety and efficacy.

We have had some experience with this in some bilateral agreements and we feel that we would be able to handle this, but we would look forward to your advice on it.

The CHAIRMAN. Let me follow up on your answer, and this will be my last question for now. Critics of export reform use the term "safe and effective" as if it were an absolute standard, representing a one and only result for any given drug. I personally would like to deflate this bit of rhetorical excess and I will just ask this question.

Are you saying that a drug which is safe and effective here may legitimately not be safe and effective somewhere else, and that one that is not safe and effective here may properly be found safe and effective in another country or another nation?

Dr. YOUNG. Yes, that is correct. It really does depend on the particular population, the particular drug, the need for the drug and any variations within a subset of individuals in the world. Most importantly are the studies that would be done in relation to toxicology, and in relation to pharmaceutical availability or bioavailability.

We feel though that we would be able to rely on other agencies in different parts of the world to assess that best by having each country look at their own needs, rather than us sitting in judgment and saying this is good for country A, this is good for country B. But there are no absolute standards, and one cannot say that a drug that is unequivocally safe and effective in one part of the world would be unequivocally safe and effective in another.

The CHAIRMAN. Thank you. Let us turn to Senator Kennedy.

Senator KENNEDY. Dr. Young, I welcome you here. I am a great believer of the importance of your agency and I think over the period of years we have added additional responsibilities to your agency without increasing resources, and this I think has put additional burdens on all of the people that work in that agency trying to meet challenges which the American people expect and which we expect in the Congress, and I hope that you would always feel free to let any of us know how we can be helpful trying to make your job and the job of the agency more easier.

I do not know just at the outset, I think all of us are very much aware of the excellence which has been associated with the agency in important periods of our time. I do not know whether there is anything that you want to say quickly about how we can get more rapid approval of drugs, those that ought to be approved clearly. Do you want to just deal with that one quickly? I think it is important for us to get that on the record. We are concerned obviously about the export process, but we are also interested in what suggestions you have in terms of how to do this safely clearly, but try and be sure that the extraordinary capability of American research in these areas is going to be available to the American people.

Dr. YOUNG. I appreciate you raising that question, Senator. I too am concerned with, as the agency is concerned with, the approval of new products. We have been working on developing an action plan which we hope will identify 10 particular areas that we will focus on. The first and foremost is a new drug approval process.

We feel that major gains can be made in the process by which drugs are approved without compromising in any way the quality. We will emphasize things such as the approval of information management. We have large applications that are ponderous at times, and the NDA rewrite will help simplify this.

I am in the process of completing now the IND rewrite. We feel that both of these will be able to decrease by approximately 6 months the approval process.

We also are examining ways in which we can use our resources more effectively to increase personnel in our reviewing branches. The quality of the individuals that are within FDA is extremely high. The ability to bring new and additional highly qualified individuals to the review process will help us greatly.

Senator KENNEDY. Well, if you would keep us aware of these changes, I would certainly welcome any ideas that you have in terms of how to move it. I do not want to spend time on the drug lag issue, but I do not know whether you might be able to at least submit something to the committee of what you believe to be the current situation. We hear a great deal about it and it has been the subject of hearings in the past and I think it is just generally useful, Mr. Chairman, if we get an assessment from Dr. Young as to how you assess it at the present time. We hear a lot from other different groups and I would like you to at least address that issue and make it part of the——

Dr. YOUNG. I would certainly——

Senator KENNEDY. Not on the time now, I do not want to trespass on other people's time. We have to move along.

Dr. YOUNG. Well, I would be very happy to do that. The action plan will soon be ready and I would be delighted to brief you on that and also provide some additional information that will show you exactly where we are and the types of steps and the appropriate——

Senator KENNEDY. If you can, I think it is useful to the committee and other members, I would be interested in it, whatever you can provide on that, it would be helpful.

[EDITOR'S NOTE: In response to Senator Kennedy's request, Dr. Young supplied the committee with a copy of a publication published by the Food and Drug Administration entitled "Compendium of New Drug Approvals in Eleven Industralized Countries, 1970-1983," which due to printing limitations and in the interest of economy, was retained in the files of the committee where it may be researched upon request.]

Senator KENNEDY. Let me get your assessment of foreign countries' regulatory process in terms of meeting their own responsibility on the safety and efficacy. Can you tell us which ones are good? Do you want to make that kind of assessment or have you got guidance about how to insure that—I imagine you do not want to be in a situation—we may give it to you anyway—but you do not want to be in a situation where you are making judgments of what countries are good buys and bad buys on it. How should we address that issue if we make a judgment that we are going to perhaps make some kind of a limited change in the law?

Dr. YOUNG. If a limited change is made in the law, a way to look at this is to focus on those countries, those developed countries that primarily have regulatory——

Senator KENNEDY. But how do we know which one? Your list might be quite a bit different than somebody else's. How shall we deal with that? Should we name the countries or should we—otherwise, we set a criteria and give it to you and people do not want it—how should we deal with that?

Dr. YOUNG. I think the best way would be to have you name the countries in the bill to start out with and provide guidance by which we can work with you as we extend or delete from the list, and we would be delighted to work with you in a technical fashion to support and supply such information.

Senator KENNEDY. How many would you say now would meet that criteria?

Dr. YOUNG. There are between 14 and 18 countries that I could see that would certainly make that list. I have given you a few of these in my earlier comments, and many of the EEC countries, the European Economic Community, would fall into those categories as well as other highly developed countries such as Japan.

Senator KENNEDY. Would it make any sense to provide a tropical disease exemption?

Dr. YOUNG. I think so, Senator. I believe that some of the——

Senator KENNEDY. If you make a judgment with regards to the competency of some countries, would it make any sense to do a tropical disease exemption for the LDC's?

Dr. YOUNG. I think that in the case of meeting some of the tropical diseases in the underdeveloped world, that these are critical problems. The problems of starvation are even magnified, individuals that are inflicted with parasitic disease. It would send a signal not only for the export of such important compounds but also I think stimulate research in these areas. As a microbiologist, I have been impressed with the potential possibility of dealing with tropical diseases now, and I would certainly recommend some consideration for such a stimulation.

Senator KENNEDY. Do you want to make any comments about your own assessment of the abuses in Third World countries of the dumping of various products or your general assessment of the mal-use of product in Third World countries?

Dr. YOUNG. There are two things, Senator, that I would say. First of all, it is important for us to aid, in any way that we can, through our participation in medical organizations, the overall improvement of the health delivery systems in underdeveloped countries. More important than almost anything else is the goal of health for all by the year 2000, achieved by stimulating the developing countries' health delivery system.

I had the privilege of being in Iraq at the time of the methyl mercury poisoning in 1974, and I had a chance to look at the delivery system, and as delivery systems improve I think there will be a better use of biologicals and drugs. That is the most important issue.

A second issue is following that closely, and it is a corollary of providing good information as medicinals are exported to other countries. I believe that it is important for each corporation or each medical professional group to be responsible in providing information. I have been pleased in that sense to work with the AMA to develop an overall information network.

In regards to the charge of dumping, it is an important issue. I believe though that the biggest safeguard is the responsibility of the company itself in exporting and the standards that are set. The United States has the highest standards through FDA activities and other governmental oversights of its quality control, and I believe that standard may stand us in good stead in this fashion.

Senator KENNEDY. I have other questions, Mr. Chairman. I will submit them for the record.

The CHAIRMAN. We will keep the record open for all members of the committee for a reasonable time, certainly through the end of this week.

Senator Metzenbaum.

Senator **Kerry**. Mr. Chairman, if I may just intercede. I apologize to my colleague because I have to run to a——

The **Chairman**. Certainly.

Senator **Kerry**. Could I have unanimous consent to submit two or three questions in writing and will the record remain open for a couple of days?

The **Chairman**. Surely.

Senator **Kerry**. Thank you very much, Mr. Chairman.

[Responses of Dr. Young to questions submitted by Senators Kerry and Grassley follow:]

Dr. Young's RESPONSES TO SENATOR KERRY'S QUESTIONS

Question #2:

Please rank the following possible factors as you feel they may contribute to delays in the process of drug approvals at FDA: 1) the adequacy of FDA resources, 2) differences in the quality and quantity of safety data required compared to that requested by other nations, 3) inadequacy of data presented by petitioners. Please explain your ranking. What other factors do you feel contribute to delays relative to other countries, and how would you compare those factors to the three already mentioned?

Answer:

Before responding specifically to this question, it should be pointed out that there are many assumptions made in putting forth the question that are not necessarily correct and that are difficult to evaluate. As studies conducted by the Food and Drug Administration (FDA) have shown, the time of appearance of a particular drug is highly variable from one country to another. In general, if one looks at comparisons of the United States with any one individual country it does not appear that delays are so common or so severe. It is only when we are compared with all other countries, that is, when we are considered to be "lagging" when any one of the countries of the developed world have approved a drug before us, that we begin to look as though the process is quite slow. We do not actually know how long it takes most countries to approve a particular drug because no country publishes data describing the pace of its approval process except the United States. It is clear that we are not slow compared to certain other countries, such as the Scandinavian countries or Canada or Australia. We have traditionally been slow relative to the British yet, in 1984 the British approved fewer than 10 new chemical entities while we approved 22, so that it is entirely possible attitudes and practices are changing in Great Britain.

With that introduction, the following describes what may be the major reasons for delays in the process of drug approvals at FDA:

1) An important factor is the adequacy of FDA's resources in comparison to the task that is set before the Agency. It should be appreciated that we have a requirement that evidence of effectiveness be derived from well-controlled studies, a requirement which is not present in all countries. The drug approval process is also an extremely open process in which people can, and do, question all aspects of the process so that the need for documentation of this process are uniquely great. (This contributes a great deal to the process and we believe that this documentation is useful.)

2) It is not possible to tell whether we differ greatly in the quality and quantity of safety data required compared to that requested by other nations because no other nation states or reveals the basis for its drug approvals. It certainly appears that drugs can sometimes be approved in some European countries with a considerably smaller patient exposure than is expected here. Typically, a new chemical entity would require exposure of some 1,000 or so patients before we would feel comfortable approving it for widespread use. On the other hand, when a disease is comparably uncommon, we, like all other countries, adjust our expectations of the safety data that are needed, some "orphan" drugs have been approved with data on considerably fewer than 100 patients.

3) The adequacy of data presented by petitioners is an important determinant of how rapidly the application goes through the process. We are, in a number of ways, trying to improve the advice we give to applicants and encourage them to see us before making critical decisions about how to evaluate the drug and present the data. Improvements in the quality of presentations and in the quality of data can make a difference in the pace of review.

In sum, the listed possible reasons for delay are, in order of importance, (1) the adequacy of FDA resources, (2) the adequacy of the data presented by petitioners and (3), a far distant last, differences in the quality and quantity of safety data required compared to that requested by other nations.

Other factors that are important in the rate of approval are the kind of review and documentation that is expected at the FDA by the public and that is implied in our laws and regulations. It is also important not to take at face value the often repeated charge that drugs are regularly approved slower in this country than anywhere else because data on timing of approvals are hard to find for most countries. Drugs that are submitted first to this country often appear first here and the time of evaluation may not be so very different from country to country.

Question #3:

Please explain your surveillance system for monitoring unapproved animal drugs in the food supply. Do you feel that any changes in the existing system would be needed if the drug export provisions of the law were to be changed? Please explain the reasoning behind your answer.

Answer:

The surveillance system for monitoring both approved and unapproved animal drugs in the food supply is the Federal tissue residue program. It is a coordinated program involving both FDA and USDA and is initiated at the time of slaughter by USDA inspection and sampling of red meat and poultry under their jurisdiction.

Sampling of tissue is done according to a plan which takes into account the availability of adequate methods to detect residues at specified levels. The program is targeted toward approved drugs in approved species. Monitoring for unapproved drugs occurs only when there is bona fide evidence of such use, that there is a toxicological concern, and adequate methods exist to analyze the tissues.

When residues are found above acceptable limits, carcasses may be retained and condemned and responsible producers must submit to mandatory sampling, assuming the producers can be identified. If adequate producer identification is available, this information is forwarded to the FDA for on-the-farm followup to determine if violations of the Federal Food, Drug, and Cosmetic Act have occurred.

USDA also monitors imported meat very closely for illegal residues and only allows meat to enter the United States from countries which have comparable tissue residue monitoring programs. This would mean that, even though a drug was not approved in the United States, its use could be approved in a foreign country where adequate residue monitoring was taking place. Meat and meat products from such countries would be allowed access to U.S. markets after additional USDA inspections. For this reason, we believe changes in the existing drug export provisions of law probably would not result in any measureable increase in drug residues from imported meat and poultry.

We would suggest that USDA also be consulted on this question.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of the Assistant Secretary
for Health
Washington DC 20201

NOV 25 1985

The Honorable Orrin G. Hatch
Chairman, Committee on Labor
and Human Resources
United States Senate
Washington, D.C. 20510

Dear Mr. Chairman:

This is in follow-up to our letter of November 18 regarding questions submitted by Senator Kerry subsequent to the June 5 hearing on the export of unapproved drugs. The response to the question on biotechnology is as follows:

Question:

The notice describing the regulatory policy of the Food and Drug Administration applicable to biotechnology in general states: "With respect to international harmonization the United States is seeking to promote scientific cooperation, mutual understanding of regulatory approaches, international agreement on a range of common technical problems such as the development of consistent test guidelines, laboratory practices and principles for assessing potential risks." (49 FR 50878)

Please describe progress with respect to these efforts in the area of biotechnology.

Answer:

The Food and Drug Administration (FDA) is working to establish cooperative arrangements with other nations, particularly our trading partners, so that the products of biotechnology are regulated in a consistent and rational fashion. Particular emphasis is being placed upon the development of testing standards and the sharing of clinical data and facilities. That cooperation is exemplified by the document now being finalized by the Organization for Economic Cooperation and Development (OECD), which establishes the scientific principles that underlie the oversight of biotechnology. OECD, and the World Health Organization as well, have sponsored conferences, attended by FDA staff, that allow those involved in overseeing biotechnology to share ideas and regulatory concepts. In addition, FDA has bilateral and trilateral arrangements with sister nations that are intended to permit a greater understanding of our actions relative to the regulation of biotechnology.

If we can be of any further assistance, please let us know.

Sincerely yours,

Patricia Knight
Acting Deputy Assistant Secretary
for Legislation (Health)

Dr. Young's RESPONSES TO SENATOR GRASSLEY'S QUESTIONS

Question #1:

In last year's hearing, the question was raised as to whether biologics should be treated as carefully as drugs for purposes of export. Can you briefly review for me what the current situation is with respect to the export of biologics?

Answer #1:

Biological products while under development in the United States may be exported for investigational purposes if either of the following investigational new drug (IND) requirements are met. Biologic products may be exported under an existing IND application on file with FDA, or alternatively, in lieu of filing an IND, a written request can be made to FDA by either an authorized official of the importing government or by any person seeking to export the drug. These procedures are the same as for drugs.

The shipment of a biological product for sale in interstate or foreign commerce requires that the product be maunfactured in an FDA licensed establishment holding a current product license for the specific product. The product label must contain all prescribed information including the manufacturer's name and address and the establishment's U.S. license number.

Question #2:

Concern has been expressed here today about public health disasters which might occur, were we to allow other countries' approval systems to govern sale abroad of American-made drug products. What does the record show on this issue? Have we indeed had public health disasters as a consequence of distribution and use of american-made drugs manufactured abroad?

Answer #2:

We are unaware of any public health disaster specifically brought about by a drug manufactured abroad by an American company.

Question #3:

In testimony submitted last year for the record of the hearing held on this issue, Dr. Phil Lee stated, ". . . It would be very difficult for the FDA to develop a list of approved countries, for both technical and political reasons." Do you agree with this?

Answer #3:

Yes. As stated in prior testimony, we would be most uncomfortable to be put in the position of developing such a list and, therefore, having to make difficult, if not impossible, subjective judgments on the relative quality of drug regulatory authorities of other sovereign states. As we discussed at the recent June 5 hearing on this issue before the Committee on Labor and Human Resources, it is our view that each sovereign government has the chief responsibility for determining the types of drugs that can be imported from abroad to meet their specific needs. We believe that considerable efforts have been made by the World Health Organization (WHO) and the United States, through both bilateral and unilateral mechanisms, to disseminate vital drug information and to provide technical training and assistance to health care professionals and government authorities so that they can make informed judgments and, therefore, maintain adequate safeguards to protect the public health of their citizens. And I must emphasize, as Dr. Dunne did last year, that channels of communication between national drug regulatory authorities have improved considerably in recent years, allowing even the smallest of these authorities to assume its responsibility to select drugs for distribution in their countries.

Nevertheless, if it is decided that proposed export legislation ought to contain a list of countries, a list might be established which would include countries having certain basic regulatory approaches similar to those in the United States, while at the same time tailored to their own specific health needs.

Question #4:

Are the manufacturers able to keep track of adverse reactions to drugs not approved by the FDA, but sold abroad by American companies?

Answer #4:

Foreign countries differ greatly in their adverse reaction reporting systems. An American product sold in a foreign country should be as well evaluated as any other product sold in that country. Certain countries have excellect adverse reaction reporting systems. Thus, if an American product was shipped to one of these countries, the tracking of adverse reactions would be quite good. In countries where adverse reaction reporting systems are generally ineffective, it can be assumed that American products sold in those countries would not be tracked very well.

I would add here that based on our experience with drugs that are approved here and also enjoy a worldwide market, our impression from existing reporting patterns is that manufacturers have considerable access to foreign adverse reports. This observation is based on the fact that fully 11 percent (approximately 2500 reports) of the 1984 adverse reaction reports submitted by industry to FDA were foreign reports.

It should also be noted that FDA has access to foreign adverse reaction reports through the World Health Organization program which receives reports from some 40 countries and disseminates information to countries in this network on a regular basis.

Senator METZENBAUM. Mr. Chairman, I ask unanimous consent to submit a statement.

The CHAIRMAN. Without objection, we will place your statement in the record at an appropriate place at the beginning of the printed record.

Senator METZENBAUM. Dr. Young, I do have some questions. It is nice to see you again, since our paths cross about once a week these days.

Dr. YOUNG. Yes, sir.

Senator METZENBAUM. Between September 1983 and June 1984, the British Government was forced by a number of deaths and adverse reactions to withdraw from the market six different drugs it had previously approved. These drugs were not approved in the United States and we have our own fixed standards to thank for that. But if the proposal, this proposal were to be law, any one of those six deadly drugs which were approved and then banned in Britain could have been manufactured and exported from the United States. Would not that "Made in America" stamp under those circumstances without the approval of the FDA, could that not have created tremendous international embarrassment for us, maybe in some respects similar to the whole Bhopal tragedy?

Dr. YOUNG. I think that it is imperative that the importing country clearly understand the status of the exported drug and it should be the responsibility of the corporation and assured by the FDA to be certain that that information as I indicated there is available.

If the information clearly defines where the status of that drug is, in the case of unapproved drugs that might solve that issue. However, there will be, at times, drug approval based on limited clinical trials that will subsequently be shown to be inappropriate, and it is imperative that agencies such as FDA or the British Government or other governments recognize through postmarketing surveillance a problem and rapidly meet it.

In answer in part to one of Senator Kennedy's questions, one of the things that we will put a lot of effort on in our drug approval process is postmarketing surveillance. We want to know as rapidly as we can, not only in drugs but in foods, in devices, and in veterinary medicine, when new data requires the removal of a previously approved product. I do not look at that as a failure of the system but an early alert about a problem and a demonstration that we have dealt with it successfully.

Senator METZENBAUM. Dr. Young, no one knows better than you because it is right on the front of your desk that this question of postmarket surveillance even in our own country with respect to infant formula is a task that I for one have great difficulty with your agency on at this very moment.

Now you are talking about our exporting, American manufacturers exporting to Great Britain, to West Germany, to wherever. Now let us assume for the moment that one of those nations or a company exports to one of those countries and from there they export all over the world, postmarket surveillance, what does it mean? We find an outbreak in Bangladesh or Pakistan or Iraq or any one of a thousand other places, or Taiwan, drugs manufactured in the United States sold in Great Britain, West Germany, France, Denmark, Norway, some place and then exported. Postmarket surveillance—400 people lose their lives, 4,000 become ill. What does it do to the American image?

Dr. YOUNG. We must have as good a postmarketing surveillance system in place as possible. It will not be completely perfect and you and I have been working in partnership vigorously trying to deal with one of the issues in infant formula.

However, I would feel that it is critical to recognize that in the United States and in other countries we have acted as responsibly as possible to deal with an accident when it occurs or to most importantly try to prevent it in the upfront fashion by the normal approval process. I do believe, however, that if the importing country knows the limitations and can watch the safeguards, we can be notified, we can aid in the evaluation process and provide further data through the usual postmarketing surveillance route.

Senator METZENBAUM. If this Congress were to enact this legislation or some form of it permitting the export, a position with respect to which I have very grave reservations, but if we were, would you think that that legislation ought to provide some restraints with respect to the right and the possibility of exports occurring from the country to which we have made our exports?

Dr. YOUNG. I think that would be very difficult, Senator. Transshipment would be the responsibility of the country to which the first shipment is made and I am not sure whether the law in the United States would be legally binding on that, but if I could ask counsel to comment on that if I could, please.

Mr. SCARLETT. You include some kind of a provision in the legislation against transshipment, but I think that once the exportation is made and the product is in the foreign country you lose your ability to make the requirement stick and you lose your ability to police.

Senator METZENBAUM. Have you not just made a perfect argument of why there should not be a bill? You just made the absolute perfect argument as to why any proposal along this line cannot provide adequate safeguard. You said it in one simple sentence.

Mr. SCARLETT. I do not think that I did quite that, Senator. I think that I——

Senator METZENBAUM. Maybe unpointedly, but I think you did.

Mr. SCARLETT. I think that I pointed to certain practicalities. We have two approaches that we can use. One approach would allow relatively unlimited exportation to developed countries and not provide for any exportation to Third World countries, but there is another model which would allow exportation to Third World countries against a standard that would be applied by the Food and Drug Administration. That is another model and——

Senator METZENBAUM. That is not what we are talking about here; is it? If the Food and Drug Administration provides an approval, are you saying there are different standards for exports than that for domestic consumption? Are you implying that? Is that not what you just said?

Mr. SCARLETT. No; it would be——

Senator METZENBAUM. You said you would have a model which would make it possible to export to Third World countries. Now, to me that sounds as if some different kind of aporoval than that which would be used by the Food and Drug Administration for domestic consumption.

Mr. SCARLETT. It would be a different type of risk-benefit determination, but that would allow us to examine data and make a judgment, but by hypothesis it would not be the same kind of approval because it, by hypothesis, is not an approved drug.

Senator METZENBAUM. Let me get this straight. Now we are in a different category. Do I understand the Administration, that you are saying that they are willing to permit different standards to be applied for drugs that we export than those that we supply for domestic consumption?

Dr. YOUNG. No, Senator, that was not the thrust of Mr. Scarlett's answer, I believe. The concept is dealing with transshipment and stating that it is the Administration's opinion that it is very difficult to police an established regulation against transshipment. This has been evidenced by some of the events in the past. The Eastern European gas line would be one example of a recent problem of technological transfer.

We do believe though that the safeguards that could be developed by the importing country being a developed country with similar regulatory aspects and then their responsibility in turn in shipment to other countries would be an important principle to recognize.

Senator METZENBAUM. I know there are many witnesses today and I am due at another hearing, but I want to point out that a similar proposal was pushed in this Congress last year and the Los Angeles Times warned the proposal would turn the rest of the world into guinea pigs. The Philadelphia Inquirer called the legislation "a greed bill." The Boston Globe condemned the bill for proposing an immoral double standard. And the New York Times warned of an American-made thalidomide.

Well, I think there are many questions, many concerns and many problems in enacting legislation of this kind, and frankly I am not unaware of the action of the Secretary of Health and Human Resources who last year indicated—or I guess more recently than that, this year—today's regulations will cut as much as 6 months or 20 percent on average from the 2 years or more now required for drug approval. I think the procedures that Senator Kennedy has pointed out, the FDA's protections afforded the American public are excellent ones. My only concern is at times you do not do enough, you do not act fast enough. But beyond that point I certainly approve the general thrust of the agency's activities.

And for us to propose or to consider legislation to go around the FDA and permit exports of unapproved drugs in this Senator's opinion is—I still have very grave reservations and may feel quite a bit stronger than that.

Thank you.

[Responses of Dr. Young to questions submitted by Senator Metzenbaum follows:]

Dr. Young's RESPONSES TO SENATOR METZENBAUM'S QUESTIONS

Question #1:

Last year, the drug industry based its case for the export of unapproved drugs on the length of time it takes the FDA to approve drugs. They said it places them at a disadvantage with other countries. But isn't it true that just three months ago, Secretary Heckler announced she had published final regulations which would "dramatically speed the Federal Government's review of new drugs." Didn't the Secretary also hail these regulations as the most important change in FDA regulations in "more than 20 years" which would cut 20 percent of the approval time for new drugs? Commissioner, the Secretary has announced these dramatic new changes -- near revolutionary changes if we go buy the News Release of February 22, 1985 -- so why do we need this legislation at all?

Answer #1:

It is true that major revisions have been made to the regulations governing the review and approval process for new drugs in the United States. These revisions are expected to speed the approval of important new drugs while maintaining high safety standards. However, there are specific instances where swift approval here is irrelevant to the export question.

As I pointed out in my testimony before your Committee hearing on June 5, 1985, the United States is the only major developed nation with such restrictive export controls, and we believe there are important medical uses in foreign countries for some drugs which are not commercially available here. Furthermore, there is no reason to believe there will ever be a market for them here and, therefore, they will never be subject to the approval process in the United States. Consequently, these particular drugs would not benefit from the new regulations. These include products for the prevention and treatment of infections and parasitic diseases such as schistosomiasis, trypanosomiasis, brucellosis and cholera, which are not major health problems in this country but which pose significant world health problems. For example, nine drugs on the World Health Organization's list of essential drugs are not approved here and, therefore, not available through American manufacturers in this country.

Question #2:

How do you feel about the FDA making judgment calls on the drug approval authorities of other sovereign states? How can the FDA say here are the eight countries which protect their citizens from bad drugs and the rest of the countries do not?

Answer #2:

As stated in prior testimony, we would be most uncomfortable to be put in the position of having to make difficult, if not impossible, subjective judgments on the relative quality of drug regulatory authorities of other sovereign states.

We have previously stated our view that each sovereign government has the chief responsibility for determining the types of drugs that can be imported from abroad which meet their specific needs. To this end, considerable efforts have been made by the World Health Organization (WHO) and the United States, through both bilateral and multilateral mechanisms, to disseminate vital drug information and to provide technical training and assistance to health care professionals and government authorities so that they can make informed judgments and, therefore, maintain adequate safeguards to protect the public health of their citizens. And I must emphasize, as Dr. Dunne did last year, that channels of communication between national drug regulatory authorities have improved considerably in recent years, allowing even the smallest of these authorities to assume its responsibility to select drugs for distribution in their countries.

Nevertheless, if it is decided that proposed export legislation ought to contain a list of countries, a list might be established which would include countries having certain basic regulatory approaches similar to those in the United States, while at the same time tailored to their own specific health needs.

Question #3:

Isn't it true that this proposal as embodied in last year's bill, S. 2878, would require significant FDA resources? Can your Agency provide these resources?

Answer #3:

The Executive Branch often revises its spending plans to reflect changes in priorities and responsibilities. If an export bill is enacted, the Executive Branch would allocate available funds to meet its responsibilities.

Question #4:

How would you characterize the drug approval process in the United States? Is it excellent, good, fair? Would you trade it for the process of any other country?

Answer #4:

I would characterize the drug approval process in the United States as excellent and would not trade it for any other system.

Question #5:

The Genentech proposal would allow the export of drugs that had been voluntarily withdrawn from the U.S. market. Since FDA often allows drug companies to voluntarily pull a product from the market after safety problems have been revealed, shouldn't their export be prohibited?

Answer #5:

The export of a product that had been voluntarily withdrawn from the marketplace in the United States would have to be considered on a case-by-case basis. Several issues would enter into each decision, including the reason for the market withdrawal in the United States as well as the diseases prevalent and availability of alternative medical care in the importing country. Benefit to risk judgments in any given instance would vary from country-to-country, and from drug-to-drug. In some instances, the decision to withdraw a drug from the U.S. market is based on considerations other than safety concerns.

Clearly, we have an obligation to prevent or suspend the export of any product that we have reason to believe may be hazardous to patients, and we would act accordingly.

Question #6:

Under the Genentech proposal, a company need only have an investigational new drug (IND) exemption on file to export a drug. Since only 10 percent of the drugs tested under IND ever go on to the new drug application stage, isn't it true that the proposal provides no assurance that the exported drug will ever be approved in the United States? Also, since drugs tested under an IND are only given to small numbers of patients (a few to 300), can these tests really give any assurance that the drug is safe?

Answer #6:

The premise of the question is correct. Requiring that the exported drugs have an existing IND provides no assurance that the drugs in question will ever be approved in the United States.

It is also true that no IND can give an absolute assurance of a drug's safety. It is understood that, for any drug, adverse reactions may appear in a large post-marketing population that do not appear during clinical trials. Therefore, while the existence of an IND under which patients are being treated with a drug clearly provides some information about the safety of the drug, the amount of information is limited. It is also important to recognize that the bulk of the data collected under an IND is seen by the FDA only when a new drug application is submitted except for severe adverse reactions that must be reported promptly to the Agency.

The existence of an IND only means that there have been adequate studies conducted on animals to demonstrate that the drug is reasonably safe to test in humans under carefully controlled conditions. Preliminary testing may then provide at least some information regarding the appropriateness of considering further use of the drug in humans.

Question #7:

The Genentech proposal fails to give FDA discretion to decide whether several essentially technical criteria are met. Do you believe that FDA should have some ability to exercise judgment in approving and disapproving exports? Under the proposal, a company can export the unapproved drug unless the FDA says no within 90 days. Don't you think that FDA should have to affirmatively approve the export of unapproved drugs?

Answer #7:

I do not believe that the FDA should have the obligation to approve affirmatively the export of unapproved drugs. There is no practical (or scientific) way for us to judge the reasonableness of marketing a drug in a foreign country without a full and complete review of the available data. Moreover, it is difficult to see what our basis could be for believing that a drug could be marketed abroad when we have not yet seen data to support its marketing in the United States.

This in no sense means that a different country could not reach a different, equally valid conclusion about the appropriateness of marketing an agent within its borders. It is only to say that FDA will be placed in an impossible position if it is asked to make some judgment, without complete information, about marketing a drug under an unstated standard, and one which is different from that in the Federal Food, Drug, and Cosmetic Act. It would be inappropriate to expect us to make judgments that are both responsible and informed in the absence of complete information.

The CHAIRMAN. Thank you, Senator Metzenbaum.

We will also place a statement of Senator Quayle in the record. He cannot be here because of other obligations this morning and we will put that in the record at the appropriate place, as well.

The CHAIRMAN. Senator Simon.

Senator SIMON. Thank you, Mr. Chairman.

First, my apologies for getting here late. I was just glancing through your statement. You talk about the pharmaceutical unit of the World Health Organization. What do they do precisely? Do they make the kind of evaluations that you make, or what is their function?

Dr. YOUNG. Their function, sir, is not a regulatory agency. Its function is primarily designed to provide information to deal with the development of model principles that would be involved in the export of drugs as I enunciated and as Dr. Dunne enunciated last year in his testimony.

For example, if I could quote from his last year's testimony in the House:

> In that particular area the certification scheme which was first proposed in 1975 represents an attempt to extend and to unify schemes previously operated by the health authorities of some exporting countries that issue certificate on request to foreign importers in respect to drugs that have been subjected to statutory control. The original intention of the scheme was to provide a simple administrative mechanism whereby importing country can: First, obtain assurance that the given product has been registered in the exporting country and, if applicable, obtain information on the reasons for registry; and, second, obtain assurance that (a) the manufacturing plant in which a product is produced is subject to inspections at suitable intervals, and (b) conforms to requirements for good practices in manufacturing and quality control of drugs as recommended by WHO, and third the exchange of information and request inquiries on the implementation of inspection and controls exercised by authorities in the exporting country.[1]

WHO has also maintained and catalyzed an exchange of information, and we would be happy to provide some of that for you for the record, but it is not a regulatory agency. It is an agency that provides information and catalyzes these types of proposals.

Senator SIMON. How does a country like Guatemala or Chad, how do they assure their citizens that the drugs that they are using are safe? What happens right now?

Dr. YOUNG. Basically in every nation besides the United States that has this type of control the following occurs: The request would come in either from the nation or from the corporation to provide that particular drug.

I had an opportunity to meet with my counterpart in Japan to find out information on the way they would do it. They would get the request in, they would evaluate it, they would provide an export license based on their understanding of the need of that country, the fact that the country has asked for that and then would export this to the country that has requested it—Guatemala in your case.

The Guatemalan Government would have to explore to determine whether that drug, according to their system of health care, would be of value in treating that particular disease.

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[1] Statement before the Subcommittee on Health and Environment, U.S. House of Representatives, July 27, 1984, pp. 7–8.

Senator SIMON. But the Government of Guatemala or Chad or—and I am not picking on those two countries but any of the developing nations—they do not have the ability themselves to screen so they depend on you, they depend on Japan, they depend on West Germany or some other country for that screening process, is that correct?

Dr. YOUNG. Yes, they do on approved drugs. In the case of export of drugs not yet approved, they would have the information from a third-party source such as the AMA which collaborates with FDA on both approved and unapproved biologicals and drugs, they would have information from WHO and they could write WHO for further information.

For example, if we had perfected a vaccine for malaria which had not yet completely gone through the approval process, possibly from recombinant DNA technology, it might be possible during the 2 years in which it is still in the approval process for a country to learn information about that vaccine from its clinical trials to determine whether it would be possible to use it, to get advice from WHO and certainly from the sponsoring corporation or nation and then provide and use that information in making its decision.

Senator SIMON. Do you provide information then to WHO or to Guatemala saying this is not yet approved, or how do you——

Dr. YOUNG. Yes, we do. We provide information by routine correspondence, we exchange our formal communications. And if I could ask Dr. Nightingale, who has worked with WHO for the past 6 years, to provide information in addition to what I have said, he might be able to help you further, Senator.

Dr. NIGHTINGALE. Certainly. We do give information to individual countries directly, but we also give information to WHO which takes what we have submitted as well as the submissions of other countries and sends them out on a very regular basis.

One of the safeguards which I think should be stressed is that Dr. Dunne's office at WHO actually sends out a circular every month which compiles information sent by countries to the pharmaceutical unit. Thus there is a very quick turn-around on submissions to his office. Then if countries need more information they can get it from WHO or go directly to the country which had notified WHO.

Senator SIMON. I thank you very much.

Dr. YOUNG. He also maintains a list of essential drugs that are required in developing and in developed nations. In fact, nine of the drugs that I have listed in my testimony would be on that essential list and it provides again the conduit of information.

Senator SIMON. I thank you. I thank the Chair.

Senator KENNEDY. I am sorry my friend and colleague Senator Metzenbaum is not here. The fact is we have transferred restrictions on military sales. You know, we do not go for revocation on export, but I am sure it could be more effectively done, but we have those possibilities. It is not beyond——

Dr. YOUNG. It is not beyond the pale of reason——

Senator KENNEDY [continuing]. The transfer of very, very sensitive materials.

Dr. YOUNG. Yes.

Senator KENNEDY. In many instances it involves the most important security, secrets of this country as well. I mean just on that particular issue when you get through, but I just—it is an important question that we are going to have to address, but I think we have addressed it at other times legislatively and I think that we ought to get back to that.

The CHAIRMAN. Thank you, Senator Kennedy.

I want to thank you, Commissioner Young, for coming in and again articulating your position and the position of the administration as well as you have. We appreciate your leadership in this matter and frankly it is time we start moving and quit talking about this. So we will appreciate any and all points you give us concerning better language and accomplishing the things that really have to be done, taking into consideration our country's needs but also other countries' needs as well.

There is not anybody working on this who wants to cause any hurt to anyone. What we want to do is create better world health and in the process create jobs, and I think this type of legislation is capable of doing both of those things and many other collateral things that are perhaps of similar importance.

I want to thank you again for being here and appreciate the efforts you put forth, and we thank your colleagues.

Dr. YOUNG. Thank you, Senator. We look forward to working with you on this very important legislation.

The CHAIRMAN. We thank you, sir.

Now, our next panel will be composed of representatives from the Pharmaceutical Manufacturers Association and from two biotechnology firms.

Representing PMA is Mr. Gerald Mossinghoff, the association president; he is accompanied by Mr. David Sharrock, who is the chairman of the PMA Board Task Force on Drug Export, and president of Merrell Dow Pharmaceuticals.

Also on this panel are Mr. Robert Swanson, president of Genentech, and Mr. Tim Hart, executive director of the Association of Biotechnology Companies.

Gentlemen, we welcome you. We are going to be happy to hear your testimony today. Mr. Mossinghoff, I would like you to begin, if you will.

STATEMENTS OF GERALD J. MOSSINGHOFF, PRESIDENT, PHARMACEUTICAL MANUFACTURERS ASSOCIATION, ACCOMPANIED BY BRUCE BRENNAN, GENERAL COUNSEL; DAVID B. SHARROCK, PRESIDENT, MERRELL DOW PHARMACEUTICALS, USA, ACCOMPANIED BY ROBERT A. INGRAM, VICE PRESIDENT FOR PUBLIC AFFAIRS; ROBERT A. SWANSON, PRESIDENT, GENENTECH, INC., ACCOMPANIED BY STEPHAN LAWTON, COUNSEL; AND TIM HART, EXECUTIVE DIRECTOR, ASSOCIATION OF BIOTECHNOLOGY COMPANIES

Mr. MOSSINGHOFF. Thank you very much, Mr. Chairman.

Mr. Chairman, in the interest of time, I will just present portions of my statement and with the rest of the statement to be included in the record.

Mr. Chairman, I start my statement on the first several pages with in effect an explanation of the problem that I think was so well laid out by you and by Senator Kennedy and Senator Thurmond, and so I will skip that portion of my testimony.

The removal of the U.S. prohibition has been supported by the Senate in 1979, by the U.S. House of Representatives in 1976, as you heard by the Food and Drug Administration, and by the National Academy of Engineering, among others. On page 3 of my statement I quote the relevant portions of the National Academy of Engineering studies, and I will skip that in the interest of time, sir.

There was a study done by the West Germany authorities, Erica Reis-Arndt, which shows that 1,384 drug products were first introduced in a country other than the United States between the years 1961 and 1980. In that period, only 114 products were first introduced in the United States. This occurred despite the fact that U.S. firms led the world in new drug discoveries during this time, with 24 percent of the total, ~~well~~ ahead of France who I believe had 18 percent.

Updated figures show that the situation is much the same today. From 1982 through 1984, the U.S.-based companies introduced a total of 27 new chemical entities or NCE's worldwide; 21 of them or 78 percent were first introduced in a foreign country. In 1982, 5 of 8 were first introduced in a foreign country; in 1983 10 of 11, and in 1984 6 of 8 were first introduced abroad.

In a 1980 study, the General Accounting Office found that 13 of the 14 most important new drugs approved by the FDA from July 1975 through February 1978 were approved in at least one of five foreign countries before they were approved in the United States. Four of the five countries had shorter average approval times for these 14 drugs than did the United States.

Again, updated figures show impartially that the situation remains much the same. From 1980 through 1984, about 70 percent of the 103 new chemical entities approved in the United States were first approved abroad.

Mr. Chairman, again in the interest of time I will skip the specific examples that are included in my statement. One of those has to do with Merrell Dow and you will hear from Mr. Sharrock following my testimony.

To determine the probable impact of lifting the export ban, the Pharmaceutical Manufacturers Association performed an input-output analysis. This is a technique used by the Bureau of Economic Analysis of the Department of Commerce to describe statistically the structure of the U. S. economy.

The analysis showed that, for each additional $1 million in pharmaceutical exports, about 21 jobs are created. PMA estimates conservatively that if the export ban were lifted, pharmaceutical exports would increase by about $400 million to $500 million 5 years later. The result would be that between 7,000 and 8,800 new jobs would be created in the continental United States, and between 1,300 and 1,600 jobs in Puerto Rico. The input-output analysis that we performed was reviewed by two consulting economists, Dr. Klass of Glassman-Oliver, and Dr. Crandall of Brookings Institute.

I think the PMA analysis would track pretty well the center of the chart that you put up. Our economic studies indicate that that probably is not the most favorable situation but surely is not the most dire situation. It is probably a conservative and we think an accurate projection.

The export ban places our companies at a competitive disadvantage to their foreign competitors. The competitors, none of whose countries has a similar prohibition, are able to build facilities without restriction at home. Because the U.S. ban often forces U.S. firms to locate facilities abroad, they cannot take advantage of economies of scale. Our companies, therefore, frequently are unable to achieve the most efficient use of production resources, which makes their costs higher and reduces their competitiveness in international markets.

Once a plant is established abroad, it usually remains in operation even after the United States approves the product being produced. Production decisions entail long-range planning. By the time U.S. approval is obtained, foreign production typically is well underway and the foreign country frequently continues to be the location from which international markets, including the United States, are supplied.

The export ban has a particularly onerous impact on smaller pharmaceutical companies and on the newer biotechnology firms, as you point out in your opening statement. Many smaller companies cannot easily or economically establish manufacturing facilities abroad, and as long as their products remain unapproved in the United States they are prevented from participating in foreign markets to the obvious benefit of their competitors abroad.

Mr. Chairman, let me skip to the bottom of page 9 of my statement, to say that if this committee and other members believe that an outright repeal of the ban, which is what PMA has suggested for several years, is not approprite, we believe that the bill introduced last year by you and cosponsored by Senator Quayle, S. 2878, provides an excellent framework for resolving the issues.

That legislation would permit the export of drugs not approved by the FDA under specified conditions and many safeguards that would fully protect U.S. and foreign citizens. Under the bill, new drugs not approved by the FDA could be exported to a country listed by that agency or by the Congress for the agency as having an adequate Government health authority to approve drugs if a number of specified conditions are met.

This would in effect improve the safety and reliability of drugs exported from the United States, rather than drugs now manufactured abroad because, among other things, all of our firms in the United States must comply with the good manufacturing practices of the Food and Drug Administration, and there are several other safeguards built into the legislation.

The legislation would not affect what drugs are available anywhere in the world, because as you point out, drugs are available abroad, they can be legally sold there, they just simply cannot be exported from the United States. If they were permitted to be exported from the United States, you would bring in a whole body of safeguards, including the strict adherence to good manufacturing practices and all the rest, which would in effect assure greater safety worldwide.

While the bill, S. 2878, provides a good framework for discussion, we believe that there are some provisions that should be changed. For example, S. 2878 would require that before a new drug could be exported, an investigational new drug or IND application must be filed with the Food and Drug Administration.

As Dr. Young testified, that is a tough issue to wrestle with, but in our view this seems unnecessary because to be shipped to a country the drug must already have been approved in a country which has a sophisticated health authority to approve drugs. In such a case, no additional public health protection would be provided to the unlisted country by the filing of an IND in the United States.

The bill, S. 2878, also contains somewhat complex provisions that were intended to permit FDA approved products to be exported with the appropriate labeling translated into a foreign language. These provisions have been widely misunderstood, I think, on all sides and we believe that elimination of them would not alter the regulatory scheme that would be established by the legislation or change any of its safeguards.

We also recommend that you may wish to expand the number of countries listed in the legislation. For example, it is our conclusion that Belgium, Denmark, the Netherlands, and Norway should be added to the list of countries that have systems in place and very sophisticated personnel manning those systems to approve drugs.

Before concluding, Mr. Chairman, I would like to turn briefly to the main charge made by those who oppose lifting the export ban, namely that to do so would create some sort of a double standard, allowing drugs to be sold abroad that are not good enough to be sold to Americans.

The issue as you pointed out is not what products will be sold abroad but where those products will be manufactured. No drug not already on the market or already permitted to be sold in another country would be sold as a result of lifting the export ban.

Not one U.S. firm would sell a drug it did not already have the legal right to sell. Some drugs badly needed in other parts of the world may never be approved in this country because they treat diseases that are not common here and approval is seldom sought for drugs that are not widely used in the United States. It does not make sense to prevent such drugs from being made in this country.

Further, the United States is not the only country with a sophisticated drug approval system. Many countries in Europe and Japan have comparable systems that have comparable records of protecting their citizens.

In conclusion, Mr. Chairman, the current export ban prohibiting the export of drugs not approved by the FDA protects no one. It places U.S. pharmaceutical companies at a competitive disadvantage in international markets. It aggravates this country's already acute balance of payments and balance of trade problems, and we believe it is time to lift the export ban that forces the export of U.S. capital, technology and jobs.

Mr. Chairman, this concludes my prepared remarks and I would be pleased to respond to any questions you may have.

[The prepared statement of Mr. Mossinghoff and responses to questions submitted by Senators Metzenbaum and Kerry follow:]

STATEMENT OF

GERALD J. MOSSINGHOFF

Mr. Chairman and Members of the Labor and Human Resources Committee:

I am Gerald J. Mossinghoff, President of the Pharmaceutical Manufacturers Association. PMA represents 120 research-intensive pharmaceutical companies that develop and produce most of the prescription medicines used in the United States. I appreciate this opportunity to testify about our country's unique ban on the export of drugs not approved by the U.S. Food and Drug Administration.

United States law currently prohibits the export of any new drug that has not been approved for sale in this country. The ban was never intended by Congress, but results from a technical error made in drafting amendments to the Federal Food, Drug, and Cosmetic Act in 1938. No other major drug-producing country in the world--including Japan, Great Britain, Switzerland, West Germany and France--has a comparable prohibition. In fact, I do not know of any other country that has such a law. The ban does not affect what drugs are available anywhere in the world; its only effect is to force U.S. companies desiring to compete for international business to export capital, technology and jobs to foreign countries at a time of increasing foreign competition and unprecedented U.S. trade deficits.

The impact of stronger foreign competition was brought out by the National Academy of Engineering in a 1983 study, which pointed out that "the percentage of world pharmaceutical production occurring in the United States has fallen from 50 percent in 1962, to 38 percent in 1968, to 27 percent in 1978," and that "the U.S. share of world pharmaceutical exports has fallen from greater than 30 percent before 1960 to less than 15 percent today." The Commerce Department, in its U.S. Industrial Outlook 1985, underlined the point: U.S. drug exports were an estimated $2.7 billion in 1984, an increase of 6.5 percent, but drug imports rose 35 percent to $1.8 billion. "Should this trend continue," the Commerce Department warned, "the balance of trade in drugs and pharmaceuticals will be negative by the end of 1986." This projection is based on incomplete 1984 data. Using updated 1984 data would lead to a projection that the balance of trade in drugs and pharmaceuticals will be negative by the end of 1987.

Removal of the U.S. prohibition has been supported by the Senate in 1979 and by the U.S. House of Representatives in 1976; by the Food and Drug Administration, and by the National Academy of Engineering, among others. In its 1983 report, the National Academy of Engineering stated:

> "Due to a drafting error in the 1938 Federal Food, Drug, and Cosmetic Act, current U.S. law prohibits the export of new drugs (but not new antibiotics or biologicals) unless the FDA has previously approved these products for sale in the United States. This prohibition holds regardless of the comprehensive approval or not for marketing of a particular drug in the importing country by local regulatory authorities. This procedure provides an obvious incentive for firms of all nationalities to produce drugs outside the United States, particularly in light of the fact that FDA regulation tends to entail longer than average approval delays."

As the Academy of Engineering study concluded, current U.S. law forces U.S. pharmaceutical companies to export capital, technology and jobs to other countries in large part because drug approvals usually occur later in this country than in others.

A study by the West German authority, Erika

Reis-Arndt, shows that 1,384 drug products were first introduced in a country other than the U.S. between 1961 and 1980. In that period, only 114 products were first introduced in the U.S. This occurred despite the fact that U.S. firms led the world in new-drug discoveries during this time--with 24 percent of the total.

Updated figures show that the situation remains the same. From 1982 through 1984, United States-based companies introduced a total of 27 New Chemical Entities (NCEs) worldwide; 21 of them, or 78 percent, were first introduced in a foreign country. In 1982, five of eight NCEs introduced by U.S. companies were first introduced abroad; in 1983, ten of eleven were first introduced abroad, and in 1984, six of eight were first introduced abroad.

In a 1980 study, the General Accounting Office found that 13 of the 14 most important new drugs approved by the FDA from July 1975 through February 1978 were approved in at least one of five foreign countries before they were approved in the U.S. Four of the five countries had shorter average approval times for these 14 drugs than the U.S.

Again, updated figures show, unfortunately, that the situation remains the same. From 1980 through 1984, about 70 percent of the 103 NCEs approved in the U.S. were first approved abroad.

Some specific examples vividly illustrate the impact of this country's unique prohibition against the export of new drugs not approved for domestic sale.

In 1975, American Cyanamid Company was forced to invest $11 million to expand a pharmaceutical plant in Gosport, England, to manufacture new drugs that had not been approved in the U.S. Two of the drugs manufactured at Gosport later were approved by the FDA. Another drug--still not approved here--has been approved in more than 50 other countries, and, if and when it is approved by the FDA, Cyanamid will be faced with importing it into the U.S. from Great Britain. The Gosport plant now generates $28 million in annual sales. The plant could have been built in the U.S. for less than half of what it cost to expand the English facility, and would have been considerably cheaper to operate.

By contrast, an antibiotic developed by Cyanamid was approved in Germany a year and a half before it was approved in this country in late 1981, but because antibiotics are not subject to the U.S. export ban the company decided to supply both foreign and domestic markets from U.S. facilities. The facilities cost $40 million to build and 170 new jobs were created to make the product--all of which would have been lost to a foreign country had the export ban applied to antibiotics.

A new anti-arthritic drug developed by Merck & Co, Inc., which was first approved in Great Britain in 1977, was not approved in the U.S. until 1982. During that entire five-year period, the company had sufficient capacity in the U.S. to meet all foreign needs for the product, but the export ban precluded use of this capacity. Instead, a $27-million plant was built in Ponders End, England, to manufacture the drug. In the last five years, the facility has exported $40 million of the product to foreign markets, including $6 million to the U.S. during the past year. By contrast, Merck is now investing substantial funds in modifying existing plants and contructing new facilities in this country to manufacture an antibiotic for which approval is expected in the U.S. at least a year after approval abroad.

Merrell Dow Pharmaceuticals Inc. has had similar experiences with the export ban, as David Sharrock, the company's President, will describe in detail.

To determine the probable impact of lifting the export ban, PMA performed an input-output analysis, a technique used by the Bureau of Economic Analysis of the Commerce Department to describe statistically the input-output structure of the U.S. economy. The analysis showed that, for each additional $1 million in pharmaceutical exports, about 21 jobs would be created. PMA estimates conservatively that, if the ban were lifted, pharmaceutical exports would increase by $400 million to $500 million five years later. The result would be that between 7,000 and 8,800 new jobs would be created in the continental U.S., and between 1,300 and 1,600 new jobs would be created in Puerto Rico. The input-output analysis was reviewed by two consulting economists, Dr. Michael Klass of Glassman-Oliver Economic Consultants, Inc., and Dr. Robert Crandall of the Brookings Insitution.

The export ban places our companies at a competitive disadvantage to their foreign competitors. The competitors, none of whose countries has a similar prohibition, are able to build facilities without restriction at home. Because the U.S. ban often forces

U.S. firms to locate facilities abroad, however, they cannot take advantage of economies of scale. Our companies, therefore, frequently are unable to achieve the most efficient use of production resources, which makes their costs higher and reduces their competitiveness in international markets.

Once a plant is established abroad, it usually remains in operation even after the U.S. approves the product being produced. Production decisions entail long-range planning. By the time U.S. approval is obtained, foreign production typically is well underway and the foreign country frequently continues to be the location from which international markets--and sometimes the U.S. market as well--are supplied.

The export ban has a particularly onerous impact on smaller pharmaceutical companies and on the newer biotechnology firms. Many smaller companies cannot easily or economically establish manufacturing facilities abroad and, as long as their products remain unapproved in the U.S., they are prevented from participating in foreign markets, to the obvious benefit of their competitors abroad.

As applied to biotechnology firms, the export ban actually encourages the transfer of U.S. technology to foreign companies. For many of these firms, joint research ventures with foreign companies are frequently the best means to seek commercialization of their products abroad. Such contracts generally require that the U.S. firm provide either the drug substance under investigation or the actual manufacturing technology to produce the substance locally. Because the export ban prevents the firms from supplying bulk products, it forces them to transfer the technology to develop products from the microorganisms that were genetically engineered in this country.

PMA believes it is long past time to repeal this country's unique export ban. The solution PMA has advocated for several years is simply to permit the export of new drugs not approved in the U.S. under Section 801(d) of the Federal Food, Drug, and Cosmetic Act.

If this Committee and other Members of Congress believe such an approach is inappropriate or the problem should be solved in a different manner, however, we believe the bill, S. 2878, introduced last year by you, Mr. Chairman, and cosponsored by Senator Quayle, provides an excellent framework for resolving the issues. That legislation would permit the export of drugs not approved by the FDA under specified conditions that would fully protect U.S. and foreign citizens.

Under the bill, new drugs not approved by the FDA could be exported to a country listed by that agency as having an adequate government health authority to approve drugs, if a number of specified conditions were met. These included provisions that the drug to be exported must not have been banned in the U.S.; that it must be in accord with the specifications of the foreign purchaser; and that it must not be in conflict with the laws of the country to which it is to be exported. New drugs not approved by the FDA also could be exported to all other countries, provided they were approved in at least one of the listed countries with a sophisticated drug-approval system.

While the bill provides a good basic framework, we believe there are some provisions that need to be changed. For example, S. 2878 would require that, before a new drug could be exported to an unlisted country, an Investigational New Drug or IND application must be filed with the Food and Drug Administration. This seems unnecessary because, to be shipped to such a country, the drug must already have been approved in a listed country with a sophisticated health authority to approve drugs. In such a case, no additional public-health protection would be provided to the unlisted country by the filing of an IND in the U.S.

The bill also contains somewhat complex provisions that were intended to permit FDA-approved products to be exported with the appropriate labeling translated into a foreign language. These provisions have been widely misinterpreted, however, and in our view are unnecessary. Elimination of these labeling provisions would not alter the regulatory scheme that would be established by the legislation or change any of its safeguards.

We also recommend that Belgium, Denmark, the Netherlands and Norway be added to the list of counties that appear in Section 3 of last year's bill, S. 2878. Each of these countries has a very adequate governmental health authority to approve new drugs.

Before concluding, I would like to turn briefly to the main charge made by those who oppose lifting the export ban--namely, that to do so would create a "double standard" allowing drugs to be sold abroad that are not good enough to be sold to Americans.

The issue is not what products will be sold abroad--but where they will be manufactured. No drug not already on the market or already permitted to be sold in another country would be sold as a result of lifting the export ban. Not one U.S. firm would sell a drug it did not already have the right to sell. Some drugs badly needed in other parts of the world may never be approved in this country because they treat diseases that are not common here and approval is seldom sought for drugs that are not widely used in the United States. It does not make sense to prevent such drugs from being made in this country.

Further, the U.S. is not the only country with a sophisticated drug-approval system. Many other countries in Europe and Japan have comparable systems that have comparable records of protecting their citizens. Approval by one of these countries before a new drug not approved by the FDA could be exported from the U.S. would establish that the drug is safe and effective, and would set a standard for labeling. No added protection is provided by requiring that U.S. firms manufacture such a drug abroad, rather than at home.

The current export ban prohibiting the export of new drugs not approved by the FDA protects no one, places U.S. pharmaceutical companies at a competitive disadvantage in international markets and aggravates this country's already acute balance-of-payments problems. It is time to lift an export ban that forces the export of U.S. capital, technology and jobs.

Mr. Chairman, that concludes my prepared remarks. I will be pleased to answer any questions you and the Committee may have.

THE DELAY IN APPROVING BETA BLOCKERS IN THE UNITED STATES

The delay in approving beta-blocker drugs in the United States, in comparison with their earlier approval by other developed countries with sophisticated drug-approval systems, has caused Americans unnecessary pain, suffering and deaths.

"It is now clear that beta blockers are one of those infrequent advances that revolutionize the practice of medicine," Lawrence K. Altman wrote in The New York Times on February 2, 1982. "They are 'one of the major therapeutic advances of this century,' according to a textbook on the beta blockers by Dr. William H. Frishman, a cardiologist at Albert Einstein College of Medicine in the Bronx. And Dr. Sidney Alexander of the Lahey Clinic in Boston calls them "perhaps the most significant advance in the treatment of coronary disease since the discovery of nitroglycerin,' first used in 1879 to treat the chest pains of angina."

Beta blockers were approved for the treatment of cardiac arrythmias in the United States in 1968, three years after they were approved for that use in the United Kingdom; they were approved for the treatment of angina in the United States in 1973, seven years after they were approved for that use in the United Kingdom; they were approved for the treatment of hypertension in the United States in 1976, seven years after they were approved for that use in the United Kingdom, and they were approved to reduce the risk of death for heart attack victims in the United States in 1981, six years after they were approved for that use in Sweden.

In announcing the approval of a beta blocker to treat heart-attack victims in November 1981, Dr. Arthur Hull Hayes Jr., then Commissioner of the Food and Drug Administration, said that, as a result of the approval, 7,000 to 10,000 lives could be saved a year in the United States. Scientists in Norway who had studied the drug, according to The New York Times of October 29, 1981, estimated that approval of the drug could save the lives of 12,000 to 15,000 Americans a year. Beta blockers have been used to prevent second heart attacks in Sweden since 1975.

The American Heart Association estimates that some 1.5 million Americans suffer heart attacks each year, and that about 1 million of them survive.

The approval of beta blockers in the United States to treat hypertension in 1976 has played a key--albeit delayed--role in cutting the death rate in this country from heart disease and strokes. In 1983, according to the National Heart, Lung and Blood Institute Fiscal Year Fact Book, 1984, there were 700,000 fewer deaths from cardiovascular disease than would have occurred if the 1950 rate had continued. The National Center for Health Statistics, in Health, United States, 1984, stated:

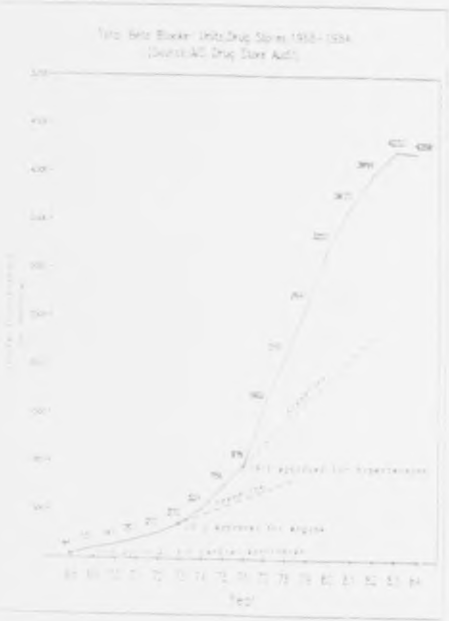
"Since the mid-1960's, mortality from heart disease has declined rapidly among all race-sex groups. Although the reasons for this decline are not entirely clear, one probable contributing factor has been a decrease in the prevalence of hypertension, which is a major risk factor for cardiovascular disease. The decline in hypertension has resulted from increased public awareness of the dangers of high blood pressure coupled with improved treatment for the condition."

In commenting on the death rate for strokes, the National Center for Health Statistics, in the same publication, stated:

"Among the major causes of death, stroke has shown the largest decrease over the past 30 years, with an especially rapid rate of decline during the 1970s. Between 1970 and 1980, the overall age-adjusted death rate for this disease decreased by 38 percent (from 66 to 41 per 100,000 population). Reasons for the dramatic decline in stroke mortality are not fully understood. Part of the decline may be attributed to better control of hypertension."

Since their delayed approval in the United States (seven years after they were approved in the United Kingdom), beta blockers have become a basic therapy for treating hypertension in this country.

It has been argued that, after beta blockers were approved for cardiac arrythmias in this country in 1968, physicians were free to use them for other indications even though such uses had not been approved by the FDA. Theoretically, this is true, but, while physicians do prescribe drugs to treat non-approved conditions to some extent, they often are reluctant to do so because of the fear of malpractice suits and the lack of directions from the FDA about appropriate use. In any case, the following chart, based on data from the IMS Drug Store Audit, clearly shows that the use of beta blockers increased substantially after they were approved in 1973 for angina and increased even more sharply again in 1976 after they were approved for the much more widespread condition of hypertension:



Thus, the delay in approving beta blockers in the United States means that thousands of Americans were denied a life-saving medicine that was being used abroad, a medicine that represented one of the major therapeutic advances of the century.

PMA ANSWERS TO QUESTIONS SUBMITTED BY SENATOR HOWARD M. METZENBAUM

Q: You indicate in your written testimony that the PMA is here today to argue for S. 2878, the Drug Export bill introduced last year. Is this the approach you support? What about the so-called Genentech compromise? Does this proposal also have your support?

A: PMA supports S. 2878 with the changes outlined in our testimony of June 5, 1985. Our Board of Directors has not taken a position on any compromise legislation, including the Genentech proposal.

Q: We've heard a lot about the jobs this bill will produce. Last year, a major drug company claimed 50,000 new jobs and nearly $2 billion in exports. Now you say $400 million in exports and 8,000 new jobs. That's a big difference. Could you elaborate on your position regarding the jobs potential of this bill?

A: We stand behind our study, in which we used an analytic technique, input-output analysis, employed by the Commerce Department's Bureau of Economic Analysis. The input-output analysis was reviewed by two consulting economists, Dr. Michael Klass of Glassman-Oliver Economic Consultants, Inc., and Dr. Robert Crandall of the Brookings Institution.

Q: The drug industry has said that the current situation with regard to drug exports is "paternalistic." How is it paternalistic to say, "We don't approve a drug in this country unless it meets our requirements, and we don't export such drugs either?"

A: The Food and Drug Administration is the best judge of the drug products that should be approved for marketing in the United States, the wealthiest country in the world, but is not the best judge of the drugs that should be approved for sale in other countries with vastly different populations, medical infrastructures, economies, health conditions and health-care needs. Each country is the best judge of the medicines that should be approved for sale in its market to meet its own special health-care needs. It is paternalistic of the United States to block the export of drugs that are needed in other countries and have been approved for sale by developed countries with sophisticated drug-approval systems.

In testifying on June 28, 1984 before the Senate Labor and Human Resources Committee on the export of drugs not approved in the United States, Dr. Mark Novitch, Acting Commissioner of the FDA, stated:

"(W)e believe that the governments of other nations are the proper authorities to assess their own health needs, the diseases and health-related characteristics of their populations, the nature of their health care delivery systems, the availability of treatment alternatives, and all of the many other factors that go into risk/benefit decisions."

Dr. Paulo de Almeida Machado, a public-health physician since 1952 who was Brazil's Minister of Health from 1974 to 1979, made the same point in testifying on June 5, 1985 on the same subject before the same Committee. He stated:

"The FDA is considered a most capable and reliable agency; an agency ensuring the best safety to the U.S. people. But the FDA is not geared towards the protection of Brazilian community interests....We need new pharmaceuticals and our needs do not match your needs. We have serious human ailments to be cured today. Other countries do not have the very same problems. We are in a hurry. Other countries may not evaluate such an urgency. Getting appropriate treatment is a human right. Appropriate means not only safe and effective, it also means early treatment."

At the same hearing, C. Payne Lucas, Executive Director of Africare, a private, non-profit organization that works to improve the quality of life in rural Africa, made the identical point. He testified:

"We believe it would be presumptive and patronizing for a regulatory body in the United States to intervene between manufacturing firms and countries in need, as regards the sale of proven medicines."

Q: Those six drugs that were approved in Britain and later withdrawn. Isn't it a good thing that Osmosin, which caused 38 deaths--was not produced in the U.S.? Isn't it a good thing that Flosint--which caused deaths and intestinal reactions--was not produced in the U.S.? And Flenac, which caused deaths and internal bleeding? Of course, the tragedy occurred anyhow. I bitterly regret it. But it did not emanate from this nation and for that I am grateful. What is your comment?

A: No drug-approval system, including that in the United States, is fool-proof. Drugs must be marketed, even after extensive pre-clinical and clinical testing, in order to more fully comprehend their safety and effectiveness. Despite differences, the drug-approval systems in Great Britain and the United States have been equally effective in ensuring the safety of their citizens. This was demonstrated in two studies.

In the May 1984 issue of *Clinical Pharmacology and Therapeutics*, Drs. Olav M. Bakke, William M. Wardell and Louis Lasagna found that the record of drug discontinuations in the U.S. and the U.K. were "remarkably similar" in the most recent decade studied--from 1974 to 1983. "It appears," the authors stated in comparing the U.S. and the U.K. drug-approval systems, "that drugs approved under modern regulations are seldom associated with unacceptable toxicity, and that the U.S. system of approval, in spite of its greater restrictiveness and insistence on detail, has not proved markedly superior in the prevention of marketing drugs that are subsequently discontinued in light of safety questions."

A January 1984 study by the Food and Drug Administration, New Drug Introductions, Discontinuations, and Safety Issues in the United States and the United Kingdom 1960-1982, reached the same conclusion. "Only 14 of the 614 NCEs introduced since 1960 were the subject of documented safety discontinuations on the U.S./U.K. two-country market," the study stated. "These 14 NCEs accounted for eight safety discontinuations in the U.S. and 10 safety discontinuations in the U.K." The study further stated: "The conclusion that documented major safety issues are not the primary reason for large differences in discontinuation rates demonstrates the need to closely examine other factors that may be accounting for the differences."

Q: Antibiotics could still be exported without restriction under this legislation. Is there any reason why antibiotics should have a total loophole in the law if drugs are restricted? Why should we have two different systems? Would you oppose a bill that included antibiotics?

A: PMA would oppose a bill that would change the current system under which unapproved antibiotics may be exported. Manufacturing facilities have been built in the United States in reliance on existing law, and the current system has worked well. There is no need to change it.

The ban prohibiting the export of new drugs not approved by the Food and Drug Administration results from a technical error made in drafting amendments to the Federal Food, Drug, and Cosmetic Act in 1938. It does not reflect the intent of Congress, which is reflected in the provisions that permit the export of unapproved antibiotics. There should be one system that permits both new drugs and antibiotics not approved by the FDA to be exported.

Q: Would the PMA support language restricting the re-export of drugs to Third World countries after they had been exported to Europe?

Q: In the course of the hearing, both the FDA Commissioner and the FDA General Counsel made the point that it would be extremely difficult to prevent the re-export or trans-shipment of drugs from countries on the approved list to countries not on the approved list--most notably those in the Third World. Do your agree or disagree?

A: The PMA Board of Directors has not taken a position on whether the research-based pharmaceutical industry would support a restriction on the re-export of drugs to developing countries after the products had been exported to Europe. PMA supports S. 2878 with the changes outlined to the Committee on June 5, 1985.

PMA agrees that it would be difficult to enforce a prohibition against the trans-shipment of drugs. It also would be unnecessary because, under S. 2878, a drug could not be shipped to an undeveloped country unless it had been approved as safe and effective in a listed, developed country with a sophisticated drug-approval system. In that case, the drug could be shipped directly to an unlisted country.

Q: Why should we rely on European drug approvals when many of the major drug disasters have occurred in Europe?

A: PMA is not aware of any studies that show that developed countries with sophisticated drug-approval systems have been less effective in recent years in protecting their citizens than the United States has been. The examples of "drug disasters" cited by opponents of export legislation either are so outdated that they are irrelevant to current practices in other developed countries with sophisticated drug-approval systems or they fail to establish that these countries are less effective than the United States in protecting their citizens. Two comprehensive studies--by Drs. Olav M. Bakke, William M. Wardell and Louis Lasagna in the May 1984 issue of *Clinical Pharmacology and Therapeutics* and the 1984 Food and Drug Administration study, *New Drug Introductions, Discontinuations, and Safety Issues in the United States and the United Kingdom 1960-1982*--conclude that the drug-approval systems in Great Britain and the United States have been equally effective in protecting their citizens. Studies also have shown that many drugs are approved abroad before they are approved in the United States, as a result of which lives may have been lost and suffering prolonged in this country.

PMA ANSWERS TO QUESTIONS SUBMITTED BY SENATOR CHARLES E. GRASSLEY

Q: Are American pharmaceutical companies able to keep track of adverse reactions to drugs not approved by FDA, but which they sell abroad? Do they make any effort to do so?

A: PMA member companies make every effort to keep track of adverse reactions to each product they make, wherever their products are sold.

Q: American Cyanamid, E.I. DuPont, and American Home Products have operations in Iowa. Can you tell me what the potential effect on these Iowa operations perpetuation of the existing situation with respect to export will have?

A: PMA does not know what specific effect the current export ban has on the Iowa operations of American Cyanamid, E.I. DuPont and American Home Products. The effect depends on individual product decisions made by the three companies. Unquestionably, however, the export ban, which no other country has, encourages U.S. pharmaceutical companies desiring to compete for international business to export capital, technology and jobs to foreign countries at a time of increasing foreign competition and unprecedented U.S. trade deficits. A PMA study showed that, if the ban were lifted, pharmaceutical exports would increase by $400 million to $500 million after five years, and between 8,300 and 10,400 new jobs would be created.

Q: Concern has been expressed here today about public health disasters which might occur were we to allow other countries' approval systems to govern sale abroad of American-made drug products. What does the record show on this issue? Have we indeed had public health disasters as a consequence of distribution and use of American-made drugs manufactured abroad?

A: The question is not whether other countries' approval systems govern the sale abroad of prescription drugs made by U.S. pharmaceutical companies. U.S. companies currently manufacture products abroad that are approved abroad but are not approved in the U.S. The question is where products approved abroad but not approved in the U.S. should be made--in a foreign country, as is required under the current export ban, or in the U.S., as PMA and the pharmaceutical industry would prefer. Were the law changed to permit the export of drugs approved abroad but not approved in the U.S., no drug not already on the market or permitted to be sold in another country would be sold as a result. Not one U.S. firm would sell a drug it did not already have the right to sell.

There have not been any public health disasters as a consequence of the distribution and use of drugs made abroad by U.S. firms. PMA member companies maintain high standards whether they make their products in the United States or in another country.

Q: Is it possible to say how much longer FDA approvals take than the approvals of other countries with what we would call sophisticated approval systems?

Why can't you just wait for FDA approval? Could you review succinctly the reasons why you feel you have to proceed before FDA approval is in hand?

Will competitors begin marketing before you are able to? Are there no safeguards, in the way of patents for instance, which would protect your investments? Or is it a case primarily of foregone income?

A: In a 1980 study, the General Accounting Office found that 13 of the 14 most important new drugs approved by the Food and Drug Administration from July 1975 through February 1978 were approved in at least one of five foreign countries before they were approved in the United States. Four of the five countries had shorter average approval times for these 14 drugs than the U.S. The average approval time was 23 months in the United States, 28 months in Sweden, 16 in Canada, 17 in Norway, 12 in Switzerland and five in the United Kingdom.

Most drugs, even those discovered and developed by U.S. companies, are introduced in a foreign country before they are introduced in the United States. A study by the West German authority, Erika Reis-Arndt, shows that 1,384 drug products were first introduced in a country other than the United States between 1961 and 1980. In that period, only 114 products were first introduced in the United States. This occurred despite the fact that U.S. firms led the world in new-drug discoveries during this time. From 1982 through 1984, U.S.-based companies introduced a total of 27 New Chemical Entities (NCEs) worldwide; 21 of them, or 78 percent, were first introduced in a foreign country. And from 1980 through 1984, about 70 percent of the 103 NCEs approved in the United States were first approved abroad.

Pharmaceutical research and developmemt is a long and expensive process that requires that decisions, particularly those concerning production, be made years in advance. In the United States, it takes seven to 10 years to discover and develop a new product and obtain approval from the Food and Drug Administration to market it, at an estimated average cost of $94 million. The pharmaceutical industry is very competitive, with companies constantly introducing new and more effective medicines. In deciding where to manufacture a product, therefore, a pharmaceutical company obviously prefers a place where it will be able to start production at the earliest time to begin to recapture its enormous R&D investment and earn a reasonable return before competitive products are launched. The current export ban--coupled with the fact that most new drugs, including those discovered by U.S. companies, are first approved abroad--pressures U.S. pharmaceutical firms to transfer capital, jobs and technology to foreign countries at a time when all are needed in the United States.

PMA (Mossinghoff) response

Question from Senator Kerry:

You have testified that no other major drug-producing country in the world has a comparable prohibition to the export of drugs. Can you provide information as to how often other nations export drugs not approved in their own country? Please provide any examples you can of such situations.

Answer:

The pharmaceutical industry does not compile statistics which relate directly to the manufacture of drugs in countries where they are not approved. However, a quick survey of some of our member companies with overseas facilities indicates that it is not an infrequent occurence for drugs to be manufactured in a country where they are not approved.

For example, Schering-Plough manufactures the drug Fulexin in Ireland and ships it to several countries although it is not approved for use there. The Lederle Laboratories division of American Cyanamid manufactures three drugs (Propranolol, Diazepam and Hydromox) in several potencies at its facility in the United Kingdom and exports them to several countries although they are not approved in the United Kingdom. Merck manufactured Enalapril in Ireland and exported it before it was approved there and manufactured and exported Nuroxin from Japan before approved there.

The **Chairman**. Thank you, Mr. Mossinghoff.

Mr. Sharrock, we will turn to you at this time. We are glad to have you here.

Mr. **Sharrock**. Thank you, Senator. It is a real pleasure to be here and we appreciate the opportunity.

I am David Sharrock, president of Merrell Dow Pharmaceuticals-U.S.A., of Cincinnati, OH. I am accompanied by Robert Ingram, Merrell Dow's vice president for public affairs.

I am also testifying today as the chairman of the PMA board of directors' Ad Hoc Committee on Export of Drugs and in support of legislation which would amend the Food and Drug Act to permit the export of new drugs that have been approved for marketing in specific foreign countries, but without approval by the U.S. Food and Drug Administration.

We obviously endorse the statement made by Mr. Mossinghoff, including the concerns regarding S. 2878.

Therefore, I need not repeat the points covered in his testimony. Rather, I appear as both a concerned private citizen and an executive in the pharmaceutical industry.

As an American concerned about the vitality of our economy, I hope I can assist this committee in recognizing the favorable impact which the removal of the present pharmaceutical export restriction would have on U.S. jobs, capital investment, and the U.S. balance of payments.

As a pharmaceutical executive, I have come here to explain to you and the committee some of the factors considered by our company and other member companies when reaching a decision about marketing a new pharmaceutical. I will focus particularly on the economically important decision of where to produce the active ingredients that go into new drugs which are approved in a foreign country. For by describing these factors, I believe you will agree that the current pharmaceutical export restriction has generally forced our member companies to preclude the United States as a possible recipient of capital investments and much needed job opportunities for our own people.

I know that a great deal has been written and said that the approval of this legislation would reduce the ability of foreign countries to protect their citizens. Therefore, at the outset, I think it is important to stress that the first and foremost consideration of our companies, when considering the introduction of a new drug, is patient safety.

Prior to seeking approval to market a new drug in any country, companies must be assured by their own experts that carefully conducted clinical trials demonstrate the safety and effectiveness of a new drug.

Consequently, at the time we reach the juncture of having both internal company assurance that a drug is safe and effective and approval to market from a foreign government with a sophisticated regulatory agency, we will proceed to market that product in that country.

At this time, candor would dictate then that the question is not whether the drug should be sold—for it has now been approved for sale—but rather where will the drug be manufactured? It is in the context of where to produce such new drugs and particularly their active ingredients that the prohibition on export of pharmaceuticals is so damaging to our country.

The current prohibition precludes in all instances even the consideration of using American facilities as a source of supply. That's correct: we cannot even include the United States in an economic evaluation because this country is precluded by the current restriction. Let me expand on this statement.

It is customary of multinational pharmaceutical companies to have facilities in major foreign countries where their drugs are sold, to carry out tableting, encapsulating, and other operations, to make finished drug dosage forms. The active ingredients, however, that go into making these finished drug dosage forms are typically produced at a small number of separate plants dedicated to manufacturing active ingredients of specific types.

The active ingredients are then shipped to the local plants producing the finished dosage forms. The larger plants producing Merrell Dow's active ingredients, for example, are located in France and Italy. One of our smaller facilities is located in the United States. Frankly, we would prefer to have a larger facility located here in the United States. The current restriction on exports precludes the consideration of such an expansion.

Now, in considering the introduction of a new drug and particularly the source of supply of the active ingredients, numerous factors must be considered, including the availability of needed equipment, labor costs, supplies of starting material, transportation, and the like.

The two key factors, however, for today's discussion are first that new drugs are generally approved for marketing outside the United States years before approval is granted in our country, and that current restrictions do not allow the active ingredients for these new drugs to be shipped out of our country prior to U.S. approval.

Let me give you an example of how these factors affect our industry by using a real situation our own company faced. At the time last year when Mr. Ingram testified before this committee in support of the removal of the existing restrictions on drug exports, we hoped to use existing plant capacity in the United States to manufacture and export the active ingredient of a new antihistamine called terfenadine, which had been approved in England, France, and West Germany in 1981 and was being marketed in more than 20 foreign countries but which had not yet been approved by the FDA.

Because the drug was not approved in the United States and since there was no legislative relief from current export restrictions, it was not possible to even consider the United States as a source of supply for these numerous foreign markets. Rather, as the drug's commercial success dramatically increased around the world, we were forced to expand production abroad to meet our increased product needs.

This set of circumstances is not unique to Merrell Dow. It is generally recognized that new drugs will be approved in foreign countries approximately 1 to 4 years earlier than in the United States. So any company introducing a new drug will face the same difficult decision of where to spend its capital and possibly create additional jobs to supply the active ingredient necessary to produce a drug first approved abroad.

Recognize also the lasting impact of these decisions, as foreign countries fiercely compete with the United States for capital investments and new jobs, these countries are prepared to create favorable economic incentives to secure such investments. Consequently, once a commitment to supply an active ingredient from a specific country is made, the approval of that drug in the United States will not bring the production of that active ingredient back to our country. My associate in other companies have similar dilemmas. While I cannot guarantee where commercial decisions which are unique to each product and to each of our companies will lead, the elimination of export restrictions to selected countries will permit us to include the United States as a candidate in our sourcing studies. This proposed legislation will remove the inequity that faces our country today.

Mr. Chairman, the American pharmaceutical industry should be able to consider America as a site to produce new drugs which are first approved in selected foreign countries, to have the option of investing capital in our own country, and of employing our own people. Current export restrictions constitute an unrealistic, self-imposed, nontariff barrier, and I urge this committee to help remove this restriction and put our country on an equal footing with our foreign competitors.

Thank you very much.

[The prepared statement of Mr. Sharrock follows:]

Merrell Dow

MERRELL DOW PHARMACEUTICALS INC.
Subsidiary of The Dow Chemical Company
P.O. Box 429553
Cincinnati, Ohio 45242-9553, U.S.A.

Telephone (513) 948-9111
Telex 214320

TESTIMONY ON THE DRUG EXPORT AMENDMENTS OF 1985

PRESENTED BY

DAVID B. SHARROCK, PRESIDENT MERRELL DOW PHARMACEUTICALS U.S.A.

COMMITTEE ON LABOR AND HUMAN RESOURCES

UNITED STATES SENATE

JUNE 5, 1985

MR. CHAIRMAN AND MEMBERS OF THE COMMITTEE:

I AM DAVID B. SHARROCK, PRESIDENT OF MERRELL DOW PHARMACEUTICALS-U.S.A., OF CINCINNATI, OHIO. I AM ACCOMPANIED BY ROBERT A. INGRAM, MERRELL DOW'S VICE PRESIDENT OF PUBLIC AFFAIRS. I AM ALSO TESTIFYING TODAY AS THE CHAIRMAN OF THE PMA BOARD OF DIRECTORS AD HOC COMMITTEE ON EXPORT OF DRUGS, AND IN SUPPORT OF LEGISLATION WHICH WOULD AMEND THE FOOD AND DRUG ACT TO PERMIT THE EXPORT OF NEW DRUGS THAT HAVE BEEN APPROVED FOR MARKETING IN SPECIFIC FOREIGN COUNTIRES, BUT WITHOUT APPROVAL BY THE U.S. FOOD AND DRUG ADMINISTRATION.

WE ENDORSE THE STATEMENT MADE BY MR. MOSSINGHOFF INCLUDING THE CONCERNS REGARDING S. 2878. THEREFORE, I NEED NOT REPEAT THE POINTS COVERED IN HIS TESTIMONY. RATHER, I APPEAR AS BOTH A CONCERNED PRIVATE CITIZEN AND AN EXECUTIVE IN THE PHARMACEUTICAL INDUSTRY.

AS AN AMERICAN CONCERNED ABOUT THE VITALITY OF OUR ECONOMY, I HOPE I CAN ASSIST THIS COMMITTEE IN RECOGNIZING THE FAVORABLE IMPACT WHICH THE REMOVAL OF THE PRESENT PHARMACEUTICAL EXPORT RESTRICTION WOULD HAVE ON U.S. JOBS, CAPITAL INVESTMENT AND THE U.S. BALANCE OF PAYMENTS.

AS A PHARMACEUTICAL EXECUTIVE I HAVE COME HERE TO EXPLAIN TO YOU AND THE COMMITTEE SOME OF THE FACTORS CONSIDERED BY OUR COMPANY AND OTHER MEMBER COMPANIES WHEN REACHING A DECISION ABOUT MARKETING A NEW PHARMACEUTICAL. I WILL FOCUS PARTICULARLY ON THE ECONOMICALLY IMPORTANT DECISION OF WHERE TO PRODUCE THE ACTIVE INGREDIENTS THAT GO INTO NEW DRUGS WHICH ARE APPROVED IN A FOREIGN COUNTRY. FOR BY DESCRIBING THESE FACTORS, I BELIEVE YOU WILL AGREE THAT THE CURRENT PHARMACEUTICAL EXPORT RESTRICTION HAS GENERALLY FORCED OUR MEMBER COMPANIES TO PRECLUDE THE U.S. AS A POSSIBLE RECIPIENT OF CAPITAL INVESTMENTS AND MUCH NEEDED JOB OPPORTUNITIES FOR OUR OWN PEOPLE.

I KNOW THAT A GREAT DEAL HAS BEEN WRITTEN AND SAID THAT THE APPROVAL OF THIS LEGISLATION WOULD REDUCE THE ABILITY OF FOREIGN COUNTRIES TO PROTECT THEIR CITIZENS. THEREFORE, AT THE OUTSET, I THINK IT'S IMPORTANT TO STRESS THAT THE FIRST AND FOREMOST CONSIDERATION OF OUR COMPANIES WHEN CONSIDERING THE INTRODUCTION OF A NEW DRUG IS PATIENT SAFETY. PRIOR TO SEEKING APPROVAL TO MARKET A NEW DRUG IN ANY COUNTRY, COMPANIES MUST BE ASSURED BY THEIR OWN EXPERTS THAT CAREFULLY CONDUCTED CLINICAL TRIALS DEMONSTRATE THE SAFETY AND EFFECTIVENESS OF THE NEW DRUG. IT IS ONLY AFTER SATISFYING THIS RESPONSIBILITY THAT APPROVAL TO MARKET IS SOUGHT IN ANY COUNTRY. FURTHERMORE, THE COUNTRIES WHICH WERE CONTAINED IN S. 2878 HAVE DEMONSTRATED THE ABILITY TO PROTECT THE WELFARE AND WELL-BEING OF THEIR

CITIZENS AND HAVE SCIENTIFICALLY AND MEDICALLY SOPHISTICATED REGULATORY AGENCIES WHICH MUST APPROVE A NEW DRUG PRIOR TO ITS SALE.

CONSEQUENTLY, AT THE TIME WE REACH THE JUNCTURE OF HAVING BOTH INTERNAL COMPANY ASSURANCES THAT A DRUG IS SAFE AND EFFECTIVE AND APPROVAL TO MARKET FROM A FOREIGN GOVERNMENT WITH A SOPHISTICATED REGULATORY AGENCY, WE WILL PROCEED TO MARKET THE PRODUCT IN THAT COUNTRY. AT THIS TIME CANDOR WOULD DICTATE THEN THAT THE QUESTION IS NOT WHETHER THE DRUG SHOULD BE SOLD — FOR IT HAS NOW BEEN APPROVED FOR SALE -- BUT RATHER WHERE WILL THE DRUG BE MANUFACTURED? IT IS IN THE CONTEXT OF WHERE TO PRODUCE SUCH NEW DRUGS AND PARTICULARLY THEIR ACTIVE INGREDIENTS, THAT THE PROHIBITION ON EXPORT OF PHARMACEUTICALS IS SO DAMAGING TO OUR COUNTRY. THE CURRENT PROHIBITION PRECLUDES IN ALL INSTANCES EVEN THE CONSIDERATION OF USING AMERICAN FACILITIES AS A SOURCE OF SUPPLY. THAT'S CORRECT: WE CANNOT EVEN INCLUDE THE U.S. IN AN ECONOMIC EVALUATION BECAUSE THIS COUNTRY IS PRECLUDED BY THE CURRENT RESTRICTION. LET ME EXPAND ON THIS STATEMENT.

IT IS CUSTOMARY OF MULTINATIONAL PHARMACEUTICAL COMPANIES TO HAVE FACILITIES IN MAJOR FOREIGN COUNTRIES WHERE THEIR DRUGS ARE SOLD, TO CARRY OUT TABLETING, ENCAPSULATING AND OTHER OPERATIONS TO MAKE FINISHED DRUG DOSAGE FORMS. THE ACTIVE INGREDIENTS, HOWEVER, THAT GO INTO MAKING THESE FINISHED DOSAGE FORMS ARE TYPICALLY PRODUCED AT A SMALL NUMBER OF SEPARATE PLANTS DEDICATED TO MANUFACTURING ACTIVE INGREDIENTS OF SPECIFIC TYPES. THE ACTIVE INGREDIENTS ARE THEN SHIPPED TO THE LOCAL PLANTS PRODUCING FINISHED DOSAGE FORMS. THE LARGER PLANTS PRODUCING MERRELL DOW'S ACTIVE INGREDIENTS, FOR EXAMPLE, ARE LOCATED IN FRANCE AND ITALY. ONE OF OUR SMALLER FACILITIES IS LOCATED IN THE U.S. FRANKLY, WE WOULD PREFER TO HAVE

A LARGER FACILITY LOCATED HERE IN THE U.S. THE CURRENT RESTRICTION ON EXPORTS PRECLUDES THE CONSIDERATION OF SUCH AN EXPANSION.

IN CONSIDERING THE INTRODUCTION OF A NEW DRUG AND PARTICULARLY THE SOURCE OF SUPPLY OF THE ACTIVE INGREDIENTS, NUMEROUS FACTORS MUST BE CONSIDERED, INCLUDING AVAILABILITY OF NEEDED EQUIPMENT, LABOR COSTS, SUPPLIES OF STARTING MATERIALS, TRANSPORTATION AND THE LIKE. THE TWO KEY FACTORS, HOWEVER, FOR TODAY'S DISCUSSION ARE FIRST THAT NEW DRUGS ARE GENERALLY APPROVED FOR MARKETING OUTSIDE THE U.S. YEARS BEFORE APPROVAL IS GRANTED IN OUR COUNTRY, AND THAT CURRENT RESTRICTIONS DO NOT ALLOW THE ACTIVE INGREDIENTS FOR THESE NEW DRUGS TO BE SHIPPED OUT OF OUR COUNTRY PRIOR TO U.S. APPROVAL. LET ME GIVE YOU AN EXAMPLE OF HOW THESE FACTORS AFFECT OUR INDUSTRY BY USING A REAL SITUATION OUR OWN COMPANY FACED.

AT THE TIME LAST YEAR WHEN MR. INGRAM TESTIFIED BEFORE THIS COMMITTEE IN SUPPORT OF THE REMOVAL OF THE EXISTING RESTRICTIONS ON DRUG EXPORTS, WE HOPED TO USE EXISTING PLANT CAPACITY IN THE U.S. TO MANUFACTURE AND EXPORT THE ACTIVE INGREDIENT FOR A NEW ANTIHISTAMINE - TERFENADINE - WHICH HAD BEEN APPROVED IN ENGLAND, FRANCE AND WEST GERMANY IN 1981, AND WAS BEING MARKETED IN MORE THAN 20 FOREIGN COUNTRIES, BUT WHICH HAD NOT YET BEEN APPROVED BY THE FDA. BECAUSE THE DRUG WAS NOT APPROVED IN THE U.S. AND SINCE THERE WAS NO LEGISLATIVE RELIEF FROM CURRENT EXPORT RESTRICTIONS, IT WAS NOT POSSIBLE TO EVEN CONSIDER THE U.S. AS A SOURCE OF SUPPLY FOR THESE NUMEROUS FOREIGN MARKETS. RATHER, AS THE DRUG'S COMMERCIAL SUCCESS DRAMATICALLY INCREASED AROUND THE WORLD, WE WERE FORCED TO EXPAND PRODUCTION ABROAD TO MEET OUR INCREASED PRODUCT NEEDS.

THIS SET OF CIRCUMSTANCES IS NOT UNIQUE TO MERRELL DOW. IT IS GENERALLY RECOGNIZED THAT NEW DRUGS WILL BE APPROVED IN FOREIGN COUNTRIES APPROXIMATELY ONE TO FOUR YEARS EARLIER THAN IN THE U.S. SO ANY COMPANY INTRODUCING A NEW DRUG WILL FACE THE SAME DIFFICULT DECISION OF WHERE TO SPEND ITS CAPITAL AND POSSIBLY CREATE ADDITIONAL JOBS, TO SUPPLY THE ACTIVE INGREDIENT NECESSARY TO PRODUCE A DRUG FIRST APPROVED ABROAD.

RECOGNIZE ALSO THE LASTING IMPACT OF THESE DECISIONS. AS FOREIGN COUNTRIES FIERCELY COMPETE WITH THE UNITED STATES FOR CAPITAL INVESTMENTS AND NEW JOBS, THESE COUNTRIES ARE PREPARED TO CREATE FAVORABLE ECONOMIC INCENTIVES TO SECURE SUCH INVESTMENTS. CONSEQUENTLY, ONCE A COMMITMENT TO SUPPLY AN ACTIVE INGREDIENT FROM A SPECIFIC COUNTRY IS MADE, THE APPROVAL OF THE DRUG IN THE UNITED STATES WILL NOT BRING THE PRODUCTION OF THAT ACTIVE INGREDIENT BACK TO OUR COUNTRY.

NOW, IF THIS LEGISLATION IS NOT ENACTED, THE NECESSITY OF EXCLUDING THE U.S. FROM CONSIDERATION AS A SOURCE OF SUPPLY OF THESE NEW DRUGS WILL CONTINUE. WE, FOR EXAMPLE, CURRENTLY HAVE TWO DRUGS WHICH SHOULD BE APPROVED FOR SALE IN EUROPEAN COUNTRIES IN THE NEXT FEW YEARS. APPROVAL IN THESE COUNTRIES IS EXPECTED IN ADVANCE OF U.S. APPROVAL. IT IS ANTICIPATED THAT THESE PRODUCTS WILL GENERATE ANNUAL SALES OUTSIDE THE U.S. IN EXCESS OF $100,000,000 BY 1993. QUITE FRANKLY, WE BELIEVE WE SHOULD BE ALLOWED TO CONSIDER THE U.S. AS A SOURCE OF SUPPLY OF THESE NEW DRUGS.

MY ASSOCIATES IN OTHER COMPANIES HAVE SIMILAR DILEMMAS. WHILE I CANNOT GUARANTEE WHERE COMMERCIAL DECISIONS WHICH ARE UNIQUE TO EACH PRODUCT AND TO EACH OF OUR COMPANIES WILL LEAD; THE ELIMINATION OF EXPORT RESTRICTIONS TO SELECTED COUNTRIES, WILL PERMIT US TO INCLUDE THE U.S. AS A CANDIDATE IN OUR SOURCING STUDIES. THIS PROPOSED LEGISLATION WILL REMOVE THE INEQUITY THAT FACES OUR COUNTRY TODAY.

MR. CHAIRMAN, THE AMERICAN PHARMACEUTICAL INDUSTRY SHOULD BE ABLE TO CONSIDER AMERICA AS A SITE TO PRODUCE NEW DRUGS WHICH ARE FIRST APPROVED IN SELECTED FOREIGN COUNTRIES, TO HAVE THE OPTION OF INVESTING CAPITAL IN OUR OWN COUNTRY AND OF EMPLOYING OUR OWN PEOPLE. CURRENT EXPORT RESTRICTIONS CONSTITUTE AN UNREALISTIC, SELF-IMPOSED, NONTARIFF BARRIER AND I URGE THIS COMMITTEE TO HELP REMOVE THIS RESTRICTION AND PUT OUR COUNTRY ON EQUAL FOOTING WITH OUR FOREIGN COMPETITORS.

Senator GRASSLEY. Thank you very much for your testimony and under direction from the chairman, who is temporarily out, I will now call on Mr. Robert Swanson, president of Genentech to be the next witness.

Mr. SWANSON. Thank you. Mr. Chairman and members of the committee, I have submitted a rather lengthy formal statement and I ask that it be included in the record and will make some brief remarks.

Senator GRASSLEY. Without objection.

Mr. SWANSON. I am Robert A. Swanson, and I am chief executive officer of Genentech, Inc., a biotechnology company principally concerned with the development of pharmaceutical products through recombinant DNA technology.

The promise of this technology for medicine, for industry and agriculture is enormous. The United States is currently the world leader in biotechnology, but our preeminent position is being threatened internationally and unless you can help, biotechnology is predestined to suffer the same international usurpation experienced by the semiconductor industry.

The overwhelming emphasis in the biotechnology industry is on pharmaceuticals, with over two-thirds of the genetic engineering companies applying their technology in this area. But current U.S. prohibitions on the export of new drugs to foreign countries are having a significant adverse impact upon the biotechnology industry in this country.

Before I go into the oversights in the Food, Drug, and Cosmetic Act which should be changed to alleviate this problem, let me tell you a little bit about Genentech and the overall biotechnology industry.

Since its founding in 1976, Genentech has grown to a firm employing over 750 people. We have genetically engineered a number of important products for medical use: TPA, a substance that dissolves blood clots which cause heart attacks; gamma interferon, an anticancer and antiviral agent; human insulin for the treatment of diabetes; human growth hormone; factor VIII, an essential blood clotting factor missing in hemophiliacs; and most recently, TNF, a promising anticancer agent. Last year alone we spent $55 million on research and development.

The biotechnology industry has grown with enormous speed from its beginnings in the midseventies to over 200 companies in the United States today. Because of public investment in basic biological research through the NIH and other agencies and strong U. S. entrepreneural spirit, our country leads the world in this new technology. However, international competition is increasing rapidly. New biotechnology companies are actually being formed by foreign governments, and there is active targeting of this industry by Japan and Western Europe.

The export restrictions are currently harming the biotechnology industry in this country. Under existing law, no drugs or biological products may be exported from the United States until the FDA has already granted approval for their marketing within the United States. This prohibition applies even when the product has already been approved by the governmental authorities of the importing country.

For example, we cannot export a medical product for use in Japan unless the FDA has first completed its approval for use here, even if the product has already been through the extensive and sophisticated approval process in Japan. No other country in the world other than the United States imposes these restrictions.

The current situation results in the loss of American jobs and the transfer of technology out of this country. It also seriously jeopardizes this Nation's competitive advantage in biotechnology.

For example, Genentech has constructed in south San Francisco what we believe to be the most advanced recombinant DNA facility in the world at the cost of tens of millions of dollars. Because of restrictions in the existing law, Genentech will not be able to export the products made in this facility to the major pharmaceutical markets in Western Europe, Canada, and Japan unless the products have been approved first within the United States.

Since only about 1 out of every 10 new drugs is approved first in the United States, to reach these overseas markets before our competitors requires the construction of new factories overseas or licensing of our technology to foreign partners. In either case, the technology, the manufacturing facility, and the jobs that go with it move outside the United States.

In recent years, the export restrictions have been widely critized by the U.S. Government itself for the reasons that I have explained. Both Houses of Congress have examined these restrictions and recommended that they be removed. Unfortunately, the two Houses have not acted at the same time.

Legislation passed by the Senate in 1979 and the bill that was passed by the House in 1976 are very close to the kind of legislation we hope will come out of these hearings.

The Senate committee report accompanying the 1979 legislation stated that "the current export policy drains technology, capital, and jobs from the United States." Others agree, including the FDA, the Department of Commerce and the Office of Technology Assessment, which itself stated that the U.S. policy "results in the transfer of technology, loss of employment opportunities for U.S. workers, and lost opportunity to help the U.S. international balance of payments."

One of the major justifications for retaining the current law is that any change will result in the dumping of drugs on Third World nations. Genentech has absolutely no intention of engaging in this unethical behavior, and we recommend legislation which safeguards against this. We merely wish to serve companies that have requested our product, well-developed nations with recognized health agencies which have approved our product and desire to use it.

In requesting amendments to the drug export law, we are seeking a law that comports with the normal marketing patterns of the overwhelming majority of new drugs. That is, they are first approved and marketed in developed countries, that is, Western Europe, Canada, and Japan, all of which have highly sophisticated medical and regulatory systems.

In most instances, it is years later, and after the product is approved in the United States, that they are marketed in other parts of the world. To withold desired products from these developed nations would constitute, in my view, a deplorable state of paternalism.

Mr. Chairman, as you know, last year Genentech and three other companies developed recommendations for legislation which became the basis for S. 2878, introduced by you and Senator Quayle. In addition, in an attempt to meet all possible concerns, and to facilitate enactment of an export bill, we have prepared and made available to you and several other Senators recommended changes in S. 2878.

The principal changes include:

One, authority for export of unapproved new drugs only to countries which are determined to have an adequate regulatory system. These countries would be listed in the legislation itself, but would be more inclusive than the eight countries listed in S. 2878.

Two, a requirement that an application to export to such countries must be filed with the Food and Drug Administration. If the application is not disapproved within 90 days, it would be deemed to have been approved and the applicant may export the drug.

Mr. Chairman, we believe that Genentech and others present a compelling case for the approval of the bill facilitating the export of new drugs. It will help stimulate an important U.S. industry, keeping our technology and jobs at home.

The need for legislation by the young, growing biotechnology companies is extremely urgent. Since I testified before your committee last summer requesting legislation, market timing for European approval of one of our products has required transfer of some production technology to Germany. We would rather be making this product in the United States. We hope that you agree and that Congress will act quickly during this session.

Thank you very much.

[The prepared statement of Mr. Swanson follows:]

Genentech, Inc.

STATEMENT OF ROBERT A. SWANSON

Mr. Chairman, and members of the committee, I am Robert A. Swanson and I am the Chief Executive Officer of Genentech, Inc., a biotechnology company principally concerned with the development and manufacture of pharmaceutical products. I appreciate this opportunity to discuss with you once again the impact of the current prohibition on the export of unapproved new drugs to foreign countries that have already approved them. Genentech believes that the existing prohibitions have a significant adverse impact upon the biotechnology industry in this country and upon the U.S. economy as a whole. We, therefore, urge adoption of an amendment to the Federal Food, Drug and Cosmetic Act which will alleviate the problems created by the present law.

The Biotechnology Industry

Before proceeding to describe the deficiencies in the existing law, permit me to discuss both Genentech and the biotechnology industry. Genentech was founded in 1976 by myself and Dr. Herbert Boyer, a scientist who three years earlier had successfully performed the first gene splicing experiment. Since then, Genentech has grown to a firm employing some 750 persons. It has genetically engineered several important products for medical use: tissue-type plasminogen activator (TPA) -- a substance that dissolves blood clots which cause heart attacks 1/; gamma interferon -- an anti-cancer and anti-viral agent; human insulin for the treatment of diabetes; human growth hormone; Factor VIII -- an essential blood clotting factor missing in hemophiliacs; and most recently, Tumor Necrosis Factor -- a promising anti-cancer agent.

Other biotechnology companies have been engaged in the production of vaccines for viral, bacterial, and parasitic diseases; improved antibodies with superior ability to detect chemical compounds and microorganisms in order to diagnose and treat diseases; and advancements in plant agriculture, including the transfer of desirable traits from one plant to another. There also are many potential environmental applications of genetic engineering, including enhancement of oil and mineral recovery, pollution control, toxic waste degradation, and crop frost resistance. 2/

1/ TPA is the subject of a randomized, double-blind, multicenter trial known as the Thrombolysis in Myocardial Infarction (TIMI) trial sponsored by the National Heart, Lung and Blood Institute. See N. Eng. J. Med. 1985; 312:932-36.

2/ Office of Technology Assessment of the Congress of the United States, Commercial Biotechnology: An International

(Footnote continued on next page)

Clearly, genetic engineering has great potential to benefit mankind. It is reasonable to expect that the fruits of genetic engineering, even in the short term, will improve the diagnosis and treatment of many diseases, will positively affect the environment, and will improve the world's food supply. Genetic engineering may be used not only as a substitute for conventional methods of manufacture, but also may be used to produce unprecedented amounts of scarce or previously unavailable biological compounds.

Since 1976, the new biotechnology industry has grown with enormous speed. Currently, over 200 companies in the United States are pursuing applications of genetic engineering. By far the greatest emphasis in the biotechnology industry is on pharmaceuticals, with over 62% of genetic engineering companies applying their technology in that area.

The biotechnology industry is roughly divided between new small firms and more diversified and established large firms. The industry now stands at a significant point in its development. The present time is particularly important for the small firms, which provide twenty-four times as many major innovations per R&D dollar as do the larger firms. 3/ Financed

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(Footnote continued from previous page)
Analysis, (U.S.G.P.O. January 1984) 6-7 and passim. (hereinafter OTA Report).

3/ OTA Report at 91-92

largely through venture capital investments, public offerings, limited partnerships and equity investments from large firms, no small firm yet has obtained income from product sales equaling even 10% of its total revenues.

The financial strain upon these small firms is related to the staggering expense and complexity of product development in this industry. Human insulin, the only recombinant DNA product that has been approved, required over 5 years to reach the market after it already had been successfully cloned. Plant costs exceeded $70 million and other expenses were well into the tens of millions of dollars. It took over 1,000 man years to bring the product through the various stages of development, starting with fermentation scale-up and purification, through animal testing and human testing, and, finally reaching FDA marketing approval.

In response to their need for capital and their inability to begin worldwide marketing, many of the small U.S. firms have begun to license their products overseas. International licensing generates the cash which is necessary for survival. This development has been controversial because some of the firms have licensed their technology to foreign firms, allowing the products to be manufactured overseas. Genentech prefers to manufacture its products in the U.S., thus keeping the technology and the jobs here and selling only the final products in bulk to the foreign firms, although as a result of current export restrictions, we have been forced to transfer some technology to our foreign partner in West Germany.

Another threat to the small firms -- a threat common to the entire genetic engineering industry -- is the keen international competition. The United States is currently the world leader, but our competitive advantage is fragile and diminishing. Japan is closing the gap at an alarming rate and is expected to catch us within two years. The Japanese government, as well as those of major competitors like Britain and West Germany, have targeted biotechnology as a key technology of the future and have made serious commitments to furthering its development. European companies have a distinct advantage over companies in the United States because many are not subject to as lengthy product approval regulation in their home country.

Simply stated, survival of many of the smaller biotechnology firms hinges largely on their ability to receive revenue by marketing their products. This in turn depends in large measure on their ability to compete for foreign markets -- principally Western Europe and Japan. We are already disadvantaged against our foreign competitors by a more time-consuming product approval process in the United States. The barriers to export of drugs which are not yet approved in this country exacerbates the situation.

Existing Law and Legislative History

Under existing law, drugs and biological products may not be exported from the United States until the Food and Drug Administration (FDA) has granted approval for their marketing within the United States. 4/ This prohibition applies even when the product in question has already been approved by the relevant governmental authorities of the importing country. Of all the major drug-producing countries in the world (the United States, Japan, Switzerland, Germany, France, and the United Kingdom), only the United States maintains these restrictions. 5/

Over the last several years, both houses of Congress have examined these restrictions, and both houses have recommended that the restrictions be removed. In 1976, as part of its revisions of the medical device law, the House adopted legislation to authorize the export of an unapproved new drug to any

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4/ See §§ 201(b), 301(d), and 505(a) of the Federal Food, Drug and Cosmetic Act (for new drugs); § 351 of the Public Health Service Act (for biological products).

5/ This export prohibition applies only to unapproved "new drugs" and not to unapproved "drugs." Under section 801(d) of the Federal Food, Drug and Cosmetic Act, an unapproved "drug" may be exported if it accords to the specifications of the foreign purchaser, is not in conflict with the laws of the foreign country to which it is intended for export, is labelled as intended for export, and is not sold or offered for sale in domestic commerce. This distinction between "drugs" and "new drugs" apparently does not represent a policy decision; rather, there is strong evidence that it is the result of an inadvertent failure to provide conforming amendments during drafting of the 1938 amendment to the Federal Food, Drug & Cosmetic Act, which introduced the concept of "new drug" into law.

country with an appropriate health agency that has reviewed and approved the drug as safe for its intended use. The legislation also authorized the export of unapproved new drugs to countries without appropriate health agencies, as long as the Secretary of the Department of Health and Human Services has determined that export of the drug is not contrary to public health and safety. The House provision was dropped in conference. 6/

Three years later, this committee and the full Senate approved a similar provision as part of The Drug Regulation Reform Act of 1979. The Senate Committee report stated that "the provisions of current law which prohibit the export of drugs which are not approved for use in the United States should be altered." 7/ The Committee determined that an appropriate balance between permitting needed export of unapproved drugs and protecting public health would be struck as long as the foreign country approved the drug and the FDA determined that export was not contrary to the public health and safety of that country. This bill was never considered by the House.

6/ See H. Conf. Rep. No. 94-1090, 94th Cong., 2nd Sess. at 65.

7/ S. Rep. No. 96-321, 96th Cong., 1st Sess. at 44. This bill abolished the distinction between "drugs" and "new drugs," and the alteration concerned "new drugs."

Thus, both houses of Congress have accepted the need to remove the strict drug export restrictions, although the two chambers have failed to act upon this conviction simultaneously.

The Food and Drug Administration has also grasped the importance of altering the existing restrictive export policy in recently amending its rules which authorize the export of unapproved new drugs for investigational purposes. Acknowledging the need to "avoid compelling American firms to export new technologies abroad," the FDA recently removed formalistic barriers to the export of investigational new drugs and biological products. 8/ Even with this welcomed change, however, only small quantities of unapproved products may be exported for investigational purposes. Of course, even this relatively minor adjustment to the export prohibitions is negated whenever the drug is approved by the importing country, since the exception only applies to experimental drugs.

Impact of the Existing Law

Current law precludes the domestic production of new drugs for export and thus results in the loss of American jobs and domestic capital investment. As demonstrated below, this conclusion is not merely ours; it is a conclusion which the Senate, the House of Representatives, the Office of Technology Assessment, the Department of Commerce, and the Food and Drug Administration have all reached over the last decade:

8/ *See* 49 Fed. Reg. 2095, January 18, 1984.

- The Senate Committee Report accompanying the Drug Regulation Reform Act of 1979 stated that "[t]he current export policy . . . drains technology, capital, and jobs from the United States." 9/
- In its 1976 assessment of the need to change our drug export policy, the [then] Interstate and Foreign Commerce Committee of the House of Representatives determined that "[b]ecause of the limitations of present law, U.S. manufacturers of [new drugs] which have been approved for use in foreign countries have constructed facilities in such countries in order to market their products." 10/
- The Office of Technology Assessment has concluded that the U.S. policy of restricting the export of unapproved drugs and biologics "results in the transfer of technology loss of employment opportunities for U.S. workers, and lost opportunity to help the U.S. international balance of payments." 11/
- The Department of Commerce made the following statement in its recent analysis of the biotechnology industry: "The most important barrier to U.S. exports is FDA regulation preventing the export of

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9/ S. Rep. No. 96-321 96th Cong., 1st Sess. at 44.

10/ H.R. No. 94-853, 94th Cong., 2nd Sess. at 57.

11/ OTA Report at 364.

any new drug until it has been approved for sale in the United States. This applies even if the product has been formally approved for marketing in the importing nation. With the delays that occur in obtaining FDA approval, U.S. firms have more incentive to manufacture new drugs abroad." 12/

- The recently-released Report of the President's Commission on Industrial Competitiveness concludes that by severely limiting the ability of American firms to market products abroad, export restrictions "threaten the United States' preeminence" in the biotechnology field. 13/

The current situation has a particularly harsh impact upon small businesses which have committed their resources within the United States. Genentech, for example, constructed the most advanced recombinant DNA facility in the world at a cost of tens of millions of dollars several years ago. This facility is located in South San Francisco, California and already employs hundreds of people. Because of the restrictions of existing law, Genentech is not able to export the products made

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12/ Department of Commerce, An Assessment of U.S. Competitiveness in High Technology Industry.

13/ President's Commission on Industrial Competitiveness, Global Competition: The New Reality. Washington: Government Printing Office, 1985. Vol. II, p. 281.

in this facility to the major pharmaceutical markets of Western Europe, Canada and Japan, unless the products have been approved for use within the United States. It could reach these markets under current U.S. law only by distributing its products from a foreign facility, which necessarily involves transfer of some technology, and fewer jobs in the United States.

What we fear, Mr. Chairman, is a revisitation of this country's experience with the semiconductor industry. Beginning with the invention of the transistor in 1947 by Bell Laboratories, it was American know-how that produced this revolution in technology. Using patience and ingenuity the Japanese began to copy American technology. Much of Japan's early research and development spending was, in fact, money paid to U. S. manufacturers under cross-licensing agreements. In many respects, the Japanese in effect paid Americans to do their research for them. The result was, at least until recently, a substantial chipping away at the United States lead in the worldwide semiconductor market.

There is a chilling analogy between the experience of the semiconductor in industry in the 1960s and 70s and the biotechnology industry in the 1980s. Yet the existing prohibition on the export of drugs not approved in the United States could very well force history to repeat itself by fostering the transfer of technology to our foreign counterparts. Why should the United States Congress allow another industry to lose its international lead -- especially when the lead is due to technology from basic research funded in large measure by government?

Mr. Chairman, the U.S. government should be encouraging rather than discouraging domestic capital investment and job creation through expanded exports. 14/ It should also be encouraging the growth of the biotechnology industry. Forcing the United States to relinquish its lead in biotechnology to such major competitors as Japan clearly is not in the interest of the United States.

One of the major justifications for retaining the current law is that any change will result in the "dumping" of drugs on third world nations. Genentech has absolutely no intention of engaging in such abhorrent, unethical behavior. We merely wish to pursue valuable and viable markets that have requested our product -- well-developed nations, with recognized health agencies, which have approved our product and desire to use it. In requesting amendments to the drug export law, we are

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14/ The Pharmaceutical Manufacturers Association estimates that at present there exist approximately 160,000 foreign employees of United States-based pharmaceutical companies employed in plants located abroad. See Annual Survey Report of the U. S. Pharmaceutical Industry, 1980-83, Pharmaceutical Manufacturers Association, Washington, D.C. Genentech estimates that the impact of passage of an export amendment would save from 10,000 to 20,000 jobs in the U. S. biotechnology industry alone over the next 5 years.

seeking a law that comports with the normal marketing patterns of the overwhelming majority of new drugs. That is, they are first approved and marketed in developed countries, i.e., Western Europe, Canada, or Japan, all of which have highly sophisticated medical and regulatory systems. In most instances, it is years later, and after the product is approved in the U.S., that they are marketed in other parts of the world.

It must be recognized, moreover, that the current export restrictions do not provide protection against "dumping." The restrictions notwithstanding, if a country wishes to import a particular drug product not approved in the United States, it will do so from one of our many foreign competitors. Current law, therefore, will not prevent the product from reaching the foreign country but merely ensure that it does so without the benefit of any safeguards that could be required by legislation.

Conclusion

Mr. Chairman, the restriction on the export of unapproved new drugs provides little benefit yet portends serious harm for both the nation and the pharmaceutical industry. The infant biotechnology industry is particularly vulnerable, especially the smaller, more innovative firms. We need legislation that protects the industry and the nation, while preserving the public health and safety -- and our need is an urgent one. We believe that the biotechnology pharmaceutical industry has clearly made the case for change in drug export laws in order to maintain a favorable trade balance, to encourage domestic placement of manufacturing facilities, and to retain valuable technology. We look forward to working with the distinguished members of this committee, and its staff, in developing a balanced approach that will help stimulate an important U. S. industry -- maintaining our technological vitality and keeping jobs at home.

The Chairman. Thank you, Mr. Swanson.

We will turn to you, Mr. Hart.

Mr. **Hart**. Mr. Chairman and members of the committee, my name is Tim Hart. I am the recently hired executive director of the Association of Biotechnology Companies. I would like to acknowledge for the committee the presence of our general counsel, Dr. Bruce Mackler, who is an immunologist, as well as a lawyer.

I must say, Mr. Chairman, representing essentially biotechnology's, "new kid on the block," it is a privilege for me to appear with representatives of the PMA, who have made such an outstanding commitment to the development of biotechnology, and Genentech, one of the world leaders in biotechnology.

Mr. Chairman, I have a prepared statement for the record. With your permission, I will submit it and I will summarize parts of it.

The Chairman. Without objection.

Mr. **Hart**. The Association of Biotechnology Companies was formed in late 1983 by nine small biotechnology companies—and I might add, parenthetically, that these are really small companies compared to pharmaceutical companies and even Genentech—who saw a need for an organization that would represent their point of view in particular and promote continued innovation in and expanded industrial application of the techniques and processes known as biotechnology. The growth of this organization, I think, mirrors the growth of biotechnology. From these 9 firms, in about 18 months we now number over 130 members, including by reciprocal arrangement 15 founding companies of the Association for the Advancement of British Biotechnology. So I think we are especially sensitive to the opportunities and problems of foreign competition.

I think it would be redundant in the extreme for me, Mr. Chairman, to make or to restate any of the arguments that have been made so eloquently today by this panel and by yourself.

As you pointed out, Mr. Chairman, the anomalous situation that exists under present law can frustrate treatment of nonindigenous diseases and contribute unnecessarily to the trade deficit, as well as doing unnecessary damage to our own economy.

ABC agrees with all of these arguments because the logic supporting them is undeniable. But, of all the arguments supporting this policy change, we are most sympathetic to those that speak for continued growth, diversity, and innovation in both research and development and the application of biotechnology toward bringing new products to market for the benefit of humans and animals everywhere in the world.

The biotechnological revolution has spawned what the "Pharmaceutical Representative" last December called, the second pharmacological revolution. Mr. Swanson has detailed some of the obvious advantages of improved biotechniques in the pharmaceutical area, so I will not repeat those.

Commissioner voung has also mentioned that the need to treat parasitic diseases with improved vaccines in Third World countries is one of high priority for world health organizations.

Recombinant DNA and hybridoma technologies are responsible for a large part of that revolution. The Office of Technology Assessment, as has been mentioned, has done an excellent study on that point and I will not reiterate that either.

The most salient fact, though, as far as ABC is concerned is that these basic technologies were pioneered by small, technology-oriented firms supoorted by venture capital. We believe that we speak for such firms when we say that this legislation would both help smaller technology-oriented biotech firms get their products to market and assure continued technological advances by making capital available through distribution and sale of products to that sector of the industry more oriented toward basic research.

I would like to call your attention to a portion of the OTA report in which OTA, after describing the domestic economic consequences of this particular policy, talks about its particular ramifications for smaller firms:

> These consequences can be expected to continue with respect to biotechnology products. The existence of such facilities in foreign countries may provide the large companies with at least a short-term competitive advantage over small, new biotechnology firms. The vast majority of the latter companies do not have and probably cannot afford to establish foreign facilities.
>
> In their joint ventures with large foreign companies, some new biotechology firms in the United States are required to provide bulk product produced by the microorganism to the foreign partner, which would secure necessary approvals and purify, package, and market the drug in foreign markets. If the U. S. firm is unable to provide bulk product, the foreign partner then has the right to obtain the organism for its own use. The U. S. prohibitions on the export of unapproved drugs and biologics might be one reason why a new biotechnology firm could not fulfill its agreement to supply bulk product to its foreign partner, thereby being required to transfer the organism and the technology.

The Department of Commerce has agreed in a separate study. It said:

> Large established companies have an advantage over the new biotechnology firms in their experience complying with Federal research and approval guidelines. For example, the pharmaceutical industry already is regulated extensively by the FDA and has developed procedures for assuring compliance with regulations. The newer firms, for the most part, do not have the experience, the resources, or the personnel to devote to such regulatory matters. Large companies have full-time biohazards officers and extensive medical monitoring of employees and do not have as much difficulty in meeting the NIH safety requirements. In addition, many of the newer firms underestimated the costs of regulatory compliance or do not have the necessary resources to move a product through the entire regulatory process.

Thus, Mr. Chairman, the result is especially anomalous for the smaller firm that has neither the regulatory staying power of larger firms nor the alternative of building facilities overseas. The small firm has the alternative of establishing partnerships and licensing arrangements, as hinted in the OTA report, with foreign companies to manufacture and distribute the product by, in essence exporting its technology.

This phenomenon was detailed in a recent article in the Sunday, May 19 edition of the Washington Post. If the direst predictions are realized, this continuing phenomenon will result in the evaporation of our country's established but eroding competitive advantage in biotechnology, as Mr. Swanson pointed out.

Mr. Chairman, our smaller member firms have expressed a great deal of frustration to us about this issue. As so-called startup companies with limited sources of capital, they are not big enough to build and manufacture abroad. They want to maintain their innovative stances and fill a need that larger organizations with more applied research, and profit orientation do not always necessarily fill.

They do not want, however, to bargain that advantage away to generate revenues to fund product development and research, if they can help it.

Most reliable estimates hold that there exists in Europe alone a market for therapeutic application using monoclonal antibodies that is half again as large as our own U.S. market, especially in the areas of cancer treatment and preventing rejection of transplanted organs.

It has been estimated that the monoclonal antibody market worldwide in the 1990's will be worth somewhere between $1 and $10 billion in revenue, and sales in Europe will constitute at least a quarter of that. The United States leads the world in this general area in scale of production of monoclonal antibodies. All but one of the seven companies that do such production are located here.

Because of the incentive to go abroad created by current policy, we risk losing—essentially through ventures that transfer this technology abroad, exacerbated by increasing competitiveness from foreign governments—our manufacturing base in monoclonal antibody technology.

Mr. Chairman, I have a letter from Mr. Robert Judge, who is the vice president of operations of Charles River Biotechnical Services, of Wilmington, MA. His is one of those seven firms and his letter describes in more detail the negative effects of current law. I would like to request that it be entered into the record.

The CHAIRMAN. Without objection.

[The letter referred to is a part of Mr. Hart's prepared statement.]

Mr. HART. In summary, Mr. Chairman and members of the committee, the Association of Biotechnology Companies feels strongly that existing policies concerning exportation of unapproved drugs and biologics discriminate against smaller biotechnology firms. Firms with the resources to commit to expansion can build development and production facilities overseas to escape this policy; smaller firms cannot, nor can they afford to do what it takes to secure domestic approval in all cases.

They must instead barter their technological advantage to create the capital necessary to stay in business if they are to preserve their identities. As Mr. Swanson has indicated, the results of this policy, if it is not changed, will be unfortunate.

ABC supports your bill, Mr. Chairman, as introduced late last session, and we stand ready to work with members of the committee and the Congress and their staffs to reach agreement on acceptable compromises if those are necessary to get a change in this policy. It is our hope that the Congress and the Food and Drug Administration will keep the needs and hopes of smaller, innovative biotech firms in mind in fashioning an agreeable bill.

We like your approach, Mr. Chairman, because it addresses two concerns that we have in particular: First, that opportunities to serve markets outside Europe are not foreclosed unnecessarily; and, second, that the process for allowing export of unapproved biologics, that is, assuring that proper safety requirements are met, does not become so elongated or cumbersome that it, in and of itself, operates as an effective barrier to firms with comparatively small regulatory resources.

That concludes my remarks, Mr. Chairman, and I would be happy to try to answer any questions the committee might have.

[The prepared statements of Mr. Hart follow:]

PREPARED STATEMENT OF TIM HART

Mr. Chairman and Members of the Committee on Labor and Human Resources:

My name is Tim Hart. I reside in Alexandria, Virginia, and am employed full time by the Association of Biotechnology Companies as its Executive Director. I am grateful for the opportunity to appear before you today, to express ABC's support for legislation that would amend existing law to permit members to export biological products to foreign markets without first subjecting them to laborious, lengthy, and expensive domestic review by our Food and Drug Administration.

First, a word or two about the Association. The Association of Biotechnology Companies is a business association that was founded in late 1983 by nine small biotechnology companies who saw a need for an organization that would represent their point of view in promoting continued innovation in and expanded industrial application of the techniques and processes known as biotechnology. Today, the Association represents over 130 members, including small and large biotech firms, allied industries and professionals interested in biotechnology's future, and a number of international members. All of you have been furnished a list of those members, so you can see for yourselves how diverse ABC's membership is and how broad is its commitment to biotechnology.

In view of your own fact-gathering efforts in the last Congress, Mr. Chairman, your staff's hard work this year, and the testimony already presented today, I don't need to plumb the obvious arguments in support of passage of legislation of this type. You already know, I'm certain, that both the Department of Commerce and your own Office of Technology Assessment agreed, in separate reports issued last year, that FDA regulations preventing the export of new drugs until they have been reviewed and approved under Section 505 of the Federal Food, Drug and Cosmetic Act constitute the "most important barrier" to U.S. exports in the pharmaceutical industry in general and with respect to existing and potential biotechnology applications for producing human and animal therapeutics. You've also heard that delays experienced in FDA approval of these products create a strong incentive for U.S. firms to manufacture them abroad, resulting in significant losses of domestic opportunities to create jobs, expand capital investment and prevent disadvantageous "brain drain." You, yourself, Mr. Chairman, have described eloquently the "anomalous situation" under present law that can frustrate treatment of nonindigenous diseases and contribute unnecessarily to the trade deficit, as well as doing unnecessary damage to our own economy. Our Association agrees with all of these arguments, because the logic supporting them is undeniable.

Of all arguments supporting this policy change, though, we are most sympathetic to those that speak for continued growth, diversity, and innovation in seeking to apply biotechnology to bringing new products to market for the benefit of humans and animals everywhere in the world.

In the broadest sense, biotechnology has been used by the pharmaceutical industry since the discovery and production of penicillin in the 1940's. The betrothal in the 1970's of broad advances in basic biological research and the drug development chemistry of the pharmaceutical industry has created the promise of real, novel, and exciting therapeutic products -- what the Pharmaceutical Representative last December called a "second pharmacological revolution." New knowledge obtained from recombinant DNA research -- so generously supported by Federal grants for basic research in the 1970's -- and from the use of DNA techniques will produce compounds to stimulate or retard sexual desire, human growth (to defeat dwarfing), memory, and even -- as has been publicized so widely lately -- predetermine the sex of a child. Therapeutics of the near future that are now possible with the use of biotechniques include: immuno-modulators, to treat such diseases as AIDS; neurotransmitters, to treat Alzheimer's disease and Lou Gehrig's disease; mood altering drugs ("natural," non-addictive eudorphines and enkephalins), to suppress anxiety; therapeutic monoclonetical antibodies, genetically "programmed" to kill cancer cells without harming nonmaligiant ones, or to combat infectious diseases that antibiotics cannot treat; prostoglavins, to thin or thicken blood and prevent ulcers and other inflammations; and synthetic vaccines, to immunize against herpes and to provide more complete and potent protection against other diseases.

Recombinant DNA and hybridoma technologies are responsible for a large part of this "revolution" in current pharmaceutical development and looming production. In 1983, according to OTA, sixty-two percent of 219 companies commercializing these new technologies were investigating applications in pharmaceuticals. Many were established pharmaceutical companies, undertaking licensing arrangements and joint ventures with smaller, "start-up" firms and investing heavily in their own operations and facilities to the tune of $2 billion, in 1983 and 1984, according to the Department of Commerce. OTA estimated that the pharmaceutical industry employed almost one-half of the research scientists engaged in genetic engineering.

The most salient fact, as far as we're concerned, is that these basic technologies were pioneered by small technology-oriented firms supported by venture capital. We believe that we speak for such firms when we say that this legislation would both help smaller, technology-oriented biotech firms get their products to market and assure continued technological advances by making capital available through distribution and sale of products, to that sector of the industry more oriented toward basic research.

OTA has captured the essence of the problem created for smaller biotechnology firms by this export policy, as follows:

> The U.S. policy of restricting the export of unapproved drugs and biologics is essentially based on paternalism. Many countries do not have the mechanisms either to evaluate or to regulate the quality of the drugs they import. In addition, there have

been cases of drug dumping--situations where drugs deemed unsafe or ineffective by the United States or other developed countries have been marketed in less developed countries.

This policy has several implications for U.S. companies using biotechnology, and the implications may differ depending on the size of the company. In part because of the export restrictions, several of the large U.S. pharmaceutical companies have established manufacturing facilities in foreign countries, where their products are approved or where the law permits the export of unapproved products. These actions result in the transfer of technology, lost employment opportunities for U.S. workers, and lost opportunity to help the U.S. international balance of payments. These consequences can be expected to continue with respect to biotechnology products. The existence of such facilities in foreign countries may provide the large companies with at least a short-term competitive advantage over small, new biotechnology firms (NBFs). The vast majority of the latter companies do not have and probably cannot afford to establish foreign facilities.

The export restrictions will also have an important implication for NBFs and for U.S. competitiveness in general because they may foster technology transfer to foreign companies with which they have joint ventures. In their joint ventures with large foreign companies, some NBF's in the United States are required to provide bulk product produced by the micro-organism to the foreign partner, which would secure necessary approvals and purify, package, and market the drug in foreign markets. If the U.S. firm is unable to provide bulk product, the foreign partner then has the right to obtain the organism for its own use. The U.S. prohibitions on the export of unapproved drugs and biologics might be one reason why an NBF could not fulfill its agreement to supply bulk product to its foreign partner, thereby being required to transfer the organism and the technology OTA, Commercial

> *Biotechnology: An International Perspective* (1984), p. 364.

Speaking in a more general context -- but no less appropriately -- the Department of Commerce described the squeeze current policy places on smaller firms:

> Another regulation which poses an obstacle to the commercialization of drugs made through the new biotechnologies in the prohibition against the export abroad of drugs and biologics not approved for use in the United States, even if those products have been approved for sale in other countries....
>
> Research and development and manufacturing by pharmaceutical firms isincreasingly being carried out in other countries where there are less stringent regulations. According to one study, more than $220 million in research and evelopment was spent overseas by U.S. pharmaceutical firms in 1978.
>
> Large established companies have an advantage over the new biotechnology firms in their experience complying with Federal research and approval guidelines. For example, the pharmaceutical industry already is regulated extensively by the FDA and has developed procedures for assuring compliance with regulations. The newer firms, for the most part, do not have this experience, the resources, or the personnel to devote to regulatory matters. Large companies have full-time biohazards officers and extensive medical monitoring of employees and do not have as much difficulty in meeting the NIH safety requirements. In addition, many of the newer firms underestimated the costs of regulatory compliance or do not have the necessary resources to move a product through the entire regulatory process. U.S. Dept. of Commerce, International Trade Administration, *High Technology Industries: Profiles and Outlooks -- Biotechnology* (1984), pp. 70-71.

Thus, the result is especially anomalous for the smaller firm that has insufficient regulatory "staying power:" where a larger firm that has sufficient regulatory muscle to see a new product through $74 million and 7-10 years' effort for approval, but yields to the incentive to get the same product on the market more inexpensively and faster by making and selling it abroad (because it can redirect those resources), a smaller firm, anxious to replace vanishing venture capital with revenues from product sales, can do neither.

The only other alternative, as hinted at in the quotation from the OTA report above, is to establish partnerships and licensing arrangements with foreign companies to manufacture and distribute the product abroad using, in essence, U.S.-exported technology. The Sunday, May 19, 1985 edition of the Washington Post, detailed this phenomenon--that of "technology transfer" that, if the direct predictions are realized--will result in the evaporation of our country's established, but eroding, competitive advantage in biotechnology.

Mr. Chairman, our smaller member firms have expressed a great deal of frustration to me about this issue. As so-called "start-up" companies with limited sources of capital, they are not big enough to build and manufacture abroad. They want to maintain their innovative stances and fill a need that larger organizations with more applied-research and profit orientation don't always fill -- the scientific "what-if'er", who takes risks to acquire new knowledge for its own sake. They don't want, however, to bargain that advantage away to generate revenues to fund product development and reserach -- if they can help it.

Most reliable estimates hold that there exists, in Europe alone, a market for therapeutic application using monoclonal antibodies that is half-again as large as our own U.S. market, especially in the areas of cancer treatment and preventing rejection of transplanted organs. It's been estimated that the monoclonal antibody market worldwide in the 1990's will be worth somewhere between $1 and $10 billion in revenues, and sales in Europe will consitute at least 25 percent of that. The U.S. leads the world in this general area, in scale-up production of monoclonal antibodies -- particularly for microencapsulation and hollow-fibre applications: All but one of the 7 companies that do such production are located here. Because of the incentive created by current policy, we risk losing -- essentially through ventures that transfer this technology abroad, exacerbated by increasing competitiveness from foreign governments -- our manufacturing base in monoclonal antibody technology.

Mr. Chairman, I have a letter from Mr. Robert Judge, Vice-President for Operations of Charles River Biotechnical Services, Inc., of Wilmington, Massachusetts. His is one of those seven firms and his letter describes in more detail the negative effects of current law. I'd like to request that it be entered into the record at this point.

charles river
biotechnical
services, inc.
251 Ballardvale Street
Wilmington, MA 01887
(617) 657-6500

June 3, 1985
RJJ: 85/026

Mr. Tim Hart
Executive Director
Associated Biotechnology Companies
1220 L Street, N.W.
Suite 615
Washington, D.C. 20015

Dear Tim,

Due to a previous commitment for which I must avail myself, I will be unable to attend the hearing scheduled for June 5, 1985 concerning Senator Hatch's amendment to the Federal Food, Drug, and Cosmetic Act (Reference Senate Bill 2878, July 26, 1984). I will, in any case, put forth a few statements within this letter which relates to some of the problems as we see facing our industry as a contract producer of monoclonal antibody products.

Currently there exists seven companies throughout the world that are involved in scale-up production of monoclonal antibodies, of which Charles River Biotechnical Services, Inc. is one. With the exception of only one of these companies, all are located here in the United States. Given this technology lead that we have in this country for scale-up production of monoclonal antibodies, a large market both domestic as well as international could be tapped if current regulations do not impede these US companies from contracting the production of cell derived products to include monoclonal antibodies. The monoclonal antibodies that the contract production companies will manufacture for customers will be used principally for five applications. These are:

- Diagnostics
- Therapeutics
- Imaging
- Purification
- Research

The projected sales over the next few years for contract produced monoclonal antibodies is said to be anywhere from $60 million and eventually reach $1.5 billion by 1990 as reported in a survey by Frost and Sullivan in April 1985. Once again, the United States should take advantage of this current technology edge it has in the biotechnology field while insuring the influx of foreign trade money is spent here in the USA.

The biggest concern that our prospective customers have referred to is the inordinate amount of time that it would take for the FDA to give its stamp of approval for monoclonal antibody products produced in this country for later distribution in foreign countries. The information that they have is that the FDA would require anywhere from two to six years of clinical testing before releasing the products from the United States. In the commercial marketplace, this time frame is not acceptable to produce and market a given product.

The second potential roadblock would be the cost involved to undertake these clinical trials and various esoteric test that would be required by FDA. It is realized that health, safety, and environmental regulations are an important role in the development of biotechnology produced products. It is very costly to obtain regulatory approval for these products, especially for new drug applications (taking anywhere from five to seven years and costing between $6 and $10 million dollars). Therefore, the additional time that would be required for FDA approval and its accompanying costs would prove to be extremely burdensome. If some of these uncertainties regarding FDA requirements are not settled expeditiously, it could discourage business in the USA biotechnology firms in selling their products to other countries with more favorable regulatory climates. Clarification and the updating of the export control regulations for biotechnological materials, micro-organisms, and technical data is urgently needed. Because few biotechnology products are being marketed currently, trade barriers are not yet a significant problem. It should be pointed out that in England a company called Celltech Limited has begun aggressive worldwide marketing for their contract production of cell derived products, including monoclonal antibodies. The British Government has worked closely with the development of the biotechnology field in England and has looked favorably on promoting business outside of the United Kingdom in that they have looked differently upon the way they regulate biotechnology produced products given some of their intended use. We believe that since the agency that governs the British drug and biological produced products is looked on favorably by the FDA in this country, we should take a closer look at how the British agency governs the importing and exporting of these biological produced products.

Many industrial firms are competing to exploit the biotechnology revolution, and the governments of such countries as Japan and Western European are considering ways to develop biotechnology within their own countries. Although the competitive position of the United States is currently strong, it is increasingly challenged by the aggressive growth of the biotechnology industry in foreign countries and in particular, Japan. It is not surprising that these challenges from countries such as Japan and others have established a development in commercialization of biotechnology as a national goal. It has been pointed out by others that there is a growing concern that the lead in biotechnology, currently understood to exist here in the USA, are not being translated into a competitive advantage for the US industry. In order for the United States to maintain its preeminence in the commercial application of biotechnology we need to have the cooperation of all governmental agencies.

I hope that these points can be presented to the Committee so that they may give these points their serious consideration when analyzing Senator Hatch's amendment to the "Pharmaceutical Export Amendments of 1985" as it relates to the Federal Food, Drug, and Cosmetic Act (21 USC 381). If future hearings are scheduled, I will make every attempt to have either myself or others from Charles River Biotechnical Services, Inc. present information and testimony as it relates to the exporting governing this new area of biotechnology.

Sincerely,

Robert J. Judge
Vice President
Operations

RJJ:pmb

cc: Mr. J.C. Foster
Dr. M.W. Balk

In summary, Mr. Chairman and members of the Committee, the Association of Biotechnology Companies feels strongly that existing policies concerning exportation of unapproved drugs and biologics discrimnate against smaller biotechnology firms. Firms with the resources to commit to expansion can build development and production facilities overseas to escape this policy; smaller firms cannot, nor can they afford to do what it takes to secure domestic approval. They must, instead, barter their technological advantage to create the capital necessary to stay in business, if they are to preserve their identities. The results if this policy is not changed, will be unfortunate.

ABC supports your bill, as introduced late last session, and will work with Members of Congress and their staffs to reach agreement on acceptable compromises, should they be necessary. It is our hope that the Congress and the Food and Drug Administration will keep the needs -- and hopes -- of smaller, innovative biotech firms in mind in fashioning an agreeable bill. We like your approach, Mr. Chairman, but are concerned that any final bill retain two features: First, that opportunities to serve markets outside Europe are not foreclosed unnecessarily, and, second, that the process for seeking to export unapproved biologics does not become so elongated or cumbersome that it -- in and of itself -- operates as an effective barrier to firms with comparatively small regulatory resources.

Mr. Chairman, that concludes my prepared remarks. I'd be happy to answer any questions or generate such additional information as the Committee may require.

Association of Biotechnology Companies

1220 L St. NW, Suite 615 • Washington, D.C. 20005 • (202) 842-ABC-9

President:
[illegible]
Cambridge BioScience Corp.

Vice-President:
[illegible], Ph.D.
Interferon Sciences, Inc.

Secretary:
[illegible], Ph.D.
Advanced Genetic Research Institute

Treasurer:
[illegible]
[illegible] Research Laboratories, Inc.

Executive Director:
[illegible]

General Counsel:
[illegible], Ph.D., J.D.

June 7, 1985

The Honorable Orrin Hatch
Chairman
Committee on Labor and Human Resources
United States Senate Office Building
527 Hart Senate Office Building
Washington, D.C. 20510

Dear Mr. Chairman:

Allow me to thank you more formally for the opportunity yesterday to present the Association's views on proposed legislation to permit the export of therapeutic biologics that have not undergone full FDA scrutiny. As I said in my remarks, it is our privilege, as a young organization, to join the Pharmaceutical Manufacturer's Association and Genentech in urging speedy passage by the Committee and the Senate of such legislation.

I am also writing because I feel compelled to respond to part of Dr. Wolfe's prepared testimony and to Ms. Drabble's oral testimony concerning the effect of current FDA policy on our member firms. Without intending to be the least bit impertinent, Mr. Chairman, I think their remarks are hogwash. ABC's responses to each of their contentions are set out below. I respectfully ask that they be made a part of the permanent hearing record of the Committee.

Since oral testimony summarized the points contained in Dr. Wolfe's submitted statement, I refer below to points made under item D.4, found on pages 26-28 of his statement:

Point 1: THE OFFICE OF TECHNOLOGY ASSESSMENT REPORT STANDS FOR THE PROPOSITION THAT BIOTECHNOLOGY TRANSFER ABROAD IS SPECULATIVE AND MAY EVEN BE EXCEEDED BY "REVERSE" TRANSFER.

Dr. Wolfe wholly mischaracterizes the OTA's observations and conclusions. A review of my testimony, Mr. Swanson's remarks, and Mr. Cape's prepared statement should more than refute this irresponsible implication. The effect this policy is having, and will continue to have on U.S. capabilities in domestic monoclonal antibody production is made clear in my statement and Mr. Judge's letter. Other testimony from biotech interests goes into similar detail. For a complete picture on how regulation affects our industry, I'd refer Dr. Wolfe to Chapter 15 of the OTA report, especially the section on "Control Over Exports," on pages 363-364. Finally, instead of quoting just from the Introduction to Chapter 19 - "International Technology Transfer, Investment, and Trade" - I'd encourage Dr. Wolfe to read the Findings at the end. The first paragraph in the findings reads as follows:

> Export control laws restrict outward technology transfer for national security, economic, or foreign policy reasons. Of the six countries studied, the United States is the only country that controls the export of medicines for foreign policy reasons. The United States also has imposed more far reaching controls on the export of micro-organisms than have the European nations and Japan, which appear to limit their concern to biological warfare agents. With these broader commodity controls come commensurately broader controls over the export of technical data. These controls may have a slightly adverse effect on the competitiveness of U.S. companies commercializing biotechnology because they could cause delays that result in sales being lost to foreign competitors. OTA Report, pp. 468-469 (Emphasis added.)

OTA's analysis of general trade barriers Con~~in~~cluded (on the same page cited by Dr. Wolfe) that, "[e]ven without truly novel issues, however, the existing legal framework [restricting biotechnology exports] bears examining, because it will affect *access to foreign markets and ultimately competition in industries applying biotechnology. Furthermore, the laws embodying government practices can be changed* (p. 454; *emphasis added.)* Thus, current FDA export policy is but one of a series of potential barriers to exporting domestically-produced biotech products. As I stated, technology transfer will occur -- especially between smaller firms and foreign investors and partners -- *because* of these barriers, not in spite of them.

Dr. Wolfe's statement presumes to elucidate the "real reasons" for arrangements with foreign interests, stating that "limits on drug exports have little to do with the biotech industry's motivation" for such arrangements.

Point 2. BIOTECH FIRMS NEED FOREIGN CAPITAL TO FINANCE RESEARCH BECAUSE THE FLOW OF VENTURE CAPITAL HAS SLOWED.

Of course they do, -- because, as I pointed out, current drug laws require them to submit to an average 7-10 years and an expenditure of $74 million to get a drug approved for domestic sale. It stands to reason that venture capital "slows" when a company proceeds from product discovery and development to the marketing phase. As the OTA report points out, foreign markets are attractive because those time and expense barriers do not exist.

Point 3. DOMESTIC BIOTECH FIRMS NEED FOREIGN PRODUCTION FACILITIES ESPECIALLY IN ENGINEERING AND PROCESSING, DUE TO A U.S. LAG IN THOSE FIELDS, REGARDLESS OF DRUG EXPORT LAWS.

This is perfectly true. If Dr. Wolfe and Ms. Drabble would reread Chapters 15 and 19 of the OTA report and both of the Department of Commerce reports I cited in my testimony, they'd appreciate more fully the role that domestic regulation (and regulatory uncertainty) play in our industry. They'd know, for example, that foreign governments in developed countries have adopted aggressive strategies to attract The

U.S. companies abroad -- long-term leases, low-interest loans, and the like. The lynchipin of these strategies, of course, is a more favorable and certain regulatory environment -- including the ability to bring therapeutic products into a market in a reasonable time, at reasonable cost. This strategy is wise -- capitalize on one's own better regulatory climate by providing a U.S. company with the manufacturing base and incentives necessary to capture the technology one doesn't have domestically. The British and Japanese have become leaders in scaleup and fermentation technologies using this very strategy. Finally, I'd agree with Dr. Wolfe that smaller companies suffer from a double competitive disadvantage, as my testimony shows; I'd hardly offer the domestic disadvantage as an argument, however, for denying them any relief in foreign markets.

Point 4: FOREIGN PARTNERSHIPS ALLOW U.S. COMPANIES INTO MARKETS OTHERWISE INACCESSIBLE BECAUSE THE PARTNER WANTS TO DEVELOP ITS OWN TECHNOLOGY.

Here -- unbelievably -- Dr. Wolfe engages in the sort of rhetorical double standard that he so deplores in policy. After dismissing the prospect of technology transfer as "speculative" and missing the "real reason" for foreign aggressiveness in attracting U.S. firms, he cites the strongest argument in favor of this legislation as authority against it! Foreign countries would have absolutely no interest in our companies if they could not give them something they don't already have. In the absence of finished products for export, they can have something better -- the capability to produce and sell finished products in their own countries at less cost, over the long term. To note the attractiveness of foreign markets -- which are attractive because they have fewer regulatory and economic obstacles to making and selling products at a profit -- and then to argue against a policy change in your own country that would make those markets less attractive and enable our domestic market to compete more effectively is intellectually dishonest. You market where you can sell the most for the least cost, in both time and resources, if you can. For large and small biotech firms alike, that ain't here -- and its policies like this ~~me~~ one that make it so.

Point 5: BIOTECH COMPANIES GAIN SCIENTIFIC AND PRODUCTION KNOWLEDGE THROUGH FOREIGN PARTNERSHIPS.

The obvious response is, "So What?" Small biotech firms have the "knowledge" now; that's what has made the U.S. the world leader. As OTA and Commerce have said -- and said again -- Federal support for basic biotech research has given our nation the lead in basic biotechnology. Our own industries are working hard to develop applications and market products using that basic knowledge. Certainly, U.S. biotech companies can "benefit from Japanese expertise in fermentation processes" -- at a price. In view of the maturation of the automobile industry, how high must we drive the price and mortgage the future to obtain the benefit? Detroit is now in the "Rust Belt" -- will Route 128 in Boston be in the "None Belt" in 40 years?

Point 6: TECHNOLOGY TRANSFER OCCURS THROUGH OTHER MEANS ANYWAY.

This is like saying the First Amendment sells newspapers. Talk's cheap, but you've got to get a printing press to make a profit. The real issue for the future of biotechnologically-produced therapeutics -- using monoclonal antibodies, in particular -- is who owns the technology and the means for producing it, and who benefits most from those arrangements. To acquire technologies that will create jobs, markets, and profits, other countries are wise to adjust their own trade and regulatory barriers and offer operating capital, plants, and other economic incentives to our firms -- especially if they can't find the same advantages here. Let's stop making excuses for not doing anything about it.

Patent and copyright laws exist to promote free exchange of knowledge, by assuring that no one steals from the discoverer. He or she can further promote it by offering it for sale or "rent." The Congress was not reluctant last session, to adjust patent and trademark laws to permit continued interchange and more effective competition, especially in the drug industry. Why should this policy not be changed, as well?

Dr. Wolfe concludes his reasoning with another out-of-context quote to support an illusory point. The

Commerce report does say what he says it says, in the following full paragraph:

> International controls relating to rDNA technology are essentially voluntary. Nationally, in terms of rDNA guidelines, those of the United States are the least restrictive, while Japan's are the most restrictive. Finally, a new set of factors has appeared on the regulatory scene in the United States; concern about the medical, social, moral and religious implications of the application of modern biotechnology in the discovery, testing and marketing of drugs. ITA, U.S. DEPT. OF COMMERCE, A Competitive Assessment of the U.S. Pharmaceutical Industry (1984), P. 73. (Emphasis added.)

I am compelled to attach for the record the entire section of the Report from which that single sentence was taken. It opens by describing the role that current drug export policy plays in the export, gradually, of the pharmaceutical industry's manufacturing base. It continues to point out that increasing world regulation will continue to drive up costs and discourage innovation. It concludes:

> Thus, although already highly regulated, the pharmaceutical industry will very likely be operating in an even more controlled environment during the next few years and beyond.

The concern here, relating to drug export policy, is symptomatic of the larger and overarching concern for the biotechnology industry, which is the need for regulatory certainty and consistency. It is regulatory uncertainty that is clouding the future growth of and investment in new biotechnology-derived products.

Mr. Chairman, Dr. Wolfe's final point, that our industry's case is not strong enough to outweigh "the ethical and the health and safety concerns raised by the prospect of legislating a double standard of protection," deserves reply. ABC is as concerned about the health and well-being of consumers worldwide as he is. Therapeutic products produced through applied biotechnology hold great promise for improved disease prevention and management. It goes without saying that none of our member firms would intentionally hurt anyone or expose them to needless risk. Exposing any of the world's population to a risk of death or injury without providing a benefit of great weight to justify that risk would be morally reprehensible. It is also repugnant, in our view, to deny other human beings their moral due -- respect for their own moral agency and will. Dr. Wolfe is arguing for a double standard, himself, by advocating that we continue to force our judgment -- through a policy born by accident almost 50 years ago -- on other peoples of the world, as sovereigns, no matter how great their need or willingness to accept some risk to improve the quality of life -- or perhaps its very existence -- in their own lands. It is as presumptuous to legislate the health and safety policy of other nations as it is to dictate their foreign policy. I cannot improve upon the testimony given by Dr. Machado or Mr. Lewis in support of this point.

In both his assessment of this policy's impact on our industry and his characterization of recommended legislation as a "double standard," I believe Dr. Wolfe presumes too much.

Very truly yours,

Tim Hart
Executive Director

cc: ABC Board of Directors
Members of the Committee
Bruce F. Mackler, General Counsel

TJH:dr

Other delivery systems currently being explored include pulse delivery, a method that would provide delivery in pulses (as needed in some anticancer drugs) rather than at a constant rate; an enzyme-responsive release system, e.g., using a transdermal insulin reservoir attached to the skin which would periodically take a blood sample through the pores and adjust insulin release accordingly; and computer-implants of timed-release preparations that can be adjusted as the disease condition changes. 1/ New systems that provide more accurate, site-specific and timely drug delivery, may actually lead to a reduction in the total consumption of drugs in the future.

Drug Manufacture in Space. At least two U.S. pharmaceutical companies have already made arrangements with the National Aeronautic and Space Administration (NASA) to test the manufacture of drugs in an automated factory in space. They will take advantage of the weightlessness of space to produce new medicines by the process of electrophoresis, in which molecules are electronically separated from living cells. Molecules migrate at different rates and must be separated out slowly and smoothly, a procedure that could work best in the microgravity of a factory in orbit around the earth. If the planned experiments prove to be successful, it can be expected that commercial drug manufacture will become a standard feature of future operating space stations. The technology areas described above have been largely pioneered in the United States but, in most cases, are also under vigorous development abroad.

Future Regulatory Trends

As noted earlier, the legislative mandate and regulatory procredures of the FDA evolved as a response to the perceived problems of unsafe or ineffective drugs. The regulatory system that developed in the United States has achieved a worldwide reputation for being the most stringent in terms of standards of safety and efficacy.* Added to this has been the prohibition on the export of U.S.-produced drugs that have not yet received approval from U.S. regulatory authorities. On one side of the coin, these standards (and the international reputation they enjoy) provide a competitive advantage to U.S.-based producers in foreign markets. On the other side, stringent regulatory control, with markedly longer lead times for marketing approval, may also have induced a slower rate of pharmaceutical innovation in the United States (the introduction of fewer new chemical entities) and is undoubtedly a major factor in the increasing emphasis being given by U.S. companies to drug development and manufacturing operations in their overseas subsidiaries.

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*Some Scandinavian countries have a similar reputation.

1/ Pharmaceutical Representative (PR), "25-year Outlook for Drug Development Assessed," October 1984.

It should be noted, however, that the pharmaceutical industry throughout the world has had to face increased regulation for safety and efficacy. Drug sales in West Germany slowed considerably in 1984, for example, as more drugs came under official scrutiny for review. The result of these reviews has been the recall of some 65 antiarthritic drugs produced by 33 companies and of 106 drugs that contained boric acid derivatives. 1/ The regulatory environment elsewhere in the world, moreover, often covers drug pricing as well as safety and efficiency. In Western Europe, for example, the public has called for increased supervision of drug companies as governments, trying to keep their national health care costs down, exert increased downward pressure on drug prices. Government participation in the pharmaceutical industry, in fact, appears to be increasing -- particularly in emerging nations. Even some of the industrialized nations such as Sweden, France, Italy, Canada and Australia have entered the pharmaceutical industry and trade through state-owned corporations. In many countries, the government has, or will soon become, the largest drug purchaser. These developments are likely to put further downward pressures on the prices and profit margins of pharmaceutical products sold in those countries.

International controls relating to rDNA technology are essentially voluntary. Nationally, in terms of rDNA guidelines, those of the United States are the least restrictive, while Japan's are the most restrictive. Finally, a new set of factors has appeared on the regulatory scene in the United States: concern about the medical, social, moral and religious implications of the application of modern biotechnology in the discovery, testing and marketing of drugs.

Concerns over the risks associated with rDNA technology commenced in the summer of 1971 when several scientists questioned the safety of a proposed experiment to insert a monkey tumor virus into a bacteria found in the human intestines. Committees were appointed to investigate the problem. Congress moved to develop regulations and the public at large became more involved in the debate. By 1976, scientists adopted a set of self-imposed guidelines known as the NIH guidelines and congressional and public concern abated.

In May 1984, the U.S. federal courts issued a voluntary injunction against the release of genetically engineered bacteria that would help control frost damage in plants. That decision affected only researchers receiving federal funding and not private firms. In the past, private firms have voluntarily followed the NIH guidelines and have not been regulated by the government. Yet the present case is certain to raise the issue of the appropriate role of government regulatory authority in biotechnology research.

1/ The Wall Street Journal, "West Germany Drug Industry Beseiged," May 31, 1984.

In the view of the Office of Technology Assessment report referred to above, the present regulatory system, which combines the roles and efforts of NIH and FDA, has worked quite well and does not appear to have been a major impediment to product development. It is quite clear, at the same time, that the social and ethical issues that will be raised by some of the new pharmaceutical products that may be available in the next two decades will not go away. An indication of the kind of social/ethical issue that might arise is suggested by a recent report showing a high correlation between an increase in abortions and the availability within a population group of an experimental test to determine the sex of a fetus in the early stages. The implications for public policy of the wide availability of such a product, not only on future abortion rates but of potential long-term changes in sex ratios in the general population, are profound.

Issues of safety and side effects are also bound to arise with respect to new drugs that may be produced to cure mental disorders or even such mental failings as forgetfulness. The role of the government in regulating such research and its resulting products in terms of their long-term safety and efficacy will increase. On the one hand, the demand for such products, especially those falling in the "brain-brightening" class, will be high. On the other hand, one can be sure that the public will insist on the highest standards of safety in pharmaceutical products that affect such areas of personal sensitivity as the brain and reproductive system. It will look to the government for assurance that those standards have been maintained. Thus, although already highly regulated, the pharmaceutical industry will very likely be operating in an even more controlled environment during the next few years and beyond.

Continued Internationalization of the Industry

The industrial biotechnology base in the United States today is in a state of flux. It is characterized, for example, by licensing agreements between companies and between companies and universities, by equity participation by large companies in the newer start-up companies, by joint ventures, by collaborative research between companies and between companies and universities, and by limited research and development partnerships.

The existence of these many cross-supporting arrangements indicates that most firms participating in biotechnological development of pharmaceuticals do not have the entire range of skills, i.e., technical knowledge, regulatory savoir faire, and marketing and distribution networks, to "go it alone" in the development and marketing of new drugs based on biotechnology. In addition, firms in other industrial sectors, such as chemicals and food processing, are actively pursuing opportunities in pharmaceuticals as a means of capitalizing on complementary technologies which they currently possess.

To a considerable extent, this state of flux extends to the international pharmaceutical scene. Licensing arrangements, mergers/acquisitions and joint ventures are the order of the day. American-based Merck has recently bought Banyu Seiyaku (August 1983) and has invested about $300 million in Japan. Pfizer recently acquired 100 percent of the shares of Taito. Yamanouchi Pharmaceutical Company entered into a long-term agreement with Eli Lilly under which it will provide the first selection right for marketing Yamanouchi's new drugs. Eisia and Sandoz are planning a joint venture in West Germany. Takeda Chemical Industries, in cooperation with Abbott, has been conducting R&D in the United States for antibiotics, sleeping aids, etc. Other examples abound.

Licensing from overseas is estimated to account for 10 percent of U.S. pharmaceutical sales. These arrangements can bring significant benefits to U.S. firms when the product involved is one not under in-house development or is not very far along in the development cycle. In-house research and regulatory approval can take about 10 years in the United States before a drug can be brought to market. Licensing can reduce the time by 50 percent (i.e., to 5 years). Company mergers and foreign acquisitions have increased as well. In recent years in the United States, at least 34 drug companies of modest size have merged with large companies. Also, as noted earlier, about 30 foreign-owned pharmaceutical operations, either acquired U.S firms or operating subsidiaries, are assuming increasing importance in the U.S.-based pharmaceutical industry.

It seems apparent that the pharmaceutical industry has entered an era of mounting competition and international reorganization. Two forces appear to be driving this trend: the need to share the research fruits of other companies and nations in the new biotechnology; and the need to develop, or have under license, cost-effective drugs in response to the pressures now pervasive in major markets for cost containment of health care. While the present level of international activity will undoubtedly level off at some point in the near future, there is little reason to believe, short of major change in the policies of national governments, that the international character of the pharmaceutical industry will itself diminish. The prospects, rather, are for continued internationalization of the industry in the years ahead.

The Chairman. Thank you so much. Mr. Mossinghoff, Mr. Sharrock, and Mr. Swanson, I would like to thank you for your testimony and for your continued support of the rational relaxing of our current export ban. Even the industry's critics concede that PMA has made much progress in recent years in correcting any problems which existed in questionable marketing practices abroad, and I believe the American drug industry, the pharmaceutical industry's record today is enviable.

I trust that you, Mr. Mossinghoff, will continue that positive trend as you have taken over the reins of PMA, and I look forward to working with you often in your new capacity.

I note with a great deal of interest your comments about jobs and other opportunities that could be created in this country, at no real loss from the health standpoint of people overseas, and I just feel that both yours and Mr. Sharrock's testimony were very good.

Mr. Swanson, Mr. Hart, I also want to thank you for being here. I think your testimony has been particularly important at this time because you both are in industries that are very exciting, very new and have tremendous, tremendous potential for our society as a whole and for the world as a whole. So I want to thank both of you for your interest in export reform. I am deeply impressed by the vision and potential of your biotechnology industry. I feel very good about the testimony that you have given here today.

Let me just ask a few questions. Mr. Sharrock, I have noted that the committee has received written testimony from local 12075 of the United Steelworkers of America. This particular group apparently is employed by your company. This local, of course, represents a Dow location. Did you ever have an opportunity to read their statement?

Mr. Sharrock. Yes, sir.

The Chairman. Well, what role did your company play in initiating this statement, or did you have a role?

Mr. Sharrock. It is an interesting background, Senator. I am glad you asked. When Dow acquired Merrell in 1981 and Merrell Dow was created as a subsidiary of the Dow Chemical Co., we began to receive questions from both managers and labor in the chemical facility. They would frequently ask us such things as why cannot we supply products to overseas locations, and so we began to engage in dialog and describe to them the restrictions that currently exist and eventually they decided to take a firm position and that position was sent to you and to other members of the committee in a letter that you have just referred to.

These workers truly realize that American labor is working at a disadvantage and that this legislation could help them compete on a more equal basis with foreign competitors.

The Chairman. I think they also realize that our pharmaceutical industry, in particular your company, does a very credible job, that it follows clean, scientifically sound and reasonable and good approaches and they are proud to work for the industry.

We have a number of pharmaceutical industries in my home State of Utah of which we are very proud. And we would like to see a lot more out there in Utah, naturally, because it is a good center, a good work force and our people are extremely proud of the quality control and of the whole approach toward pharmaceutical manufacturing that they have in those plants out there.

As I have visited some of the other major pharmaceutical industry plants around the Nation, I find a real esprit de corps and pride in the workers in this industry and the contributions that they really can make, but I just wanted to ask that question. It was a little tough question, but I wanted to ask it.

Mr. Mossinghoff, could you comment on your reaction to the differences between the two main alternative approaches here under consideration? Your approach of the PMA would be to just simply do away with the ban, but you realize that is going to be a very difficult thing to do legislatively perhaps.

I would like you to particularly comment with respect to providing a mechanism for export to the developing nations.

Mr. MOSSINGHOFF. Thank you, Mr. Chairman. As I have indicated in my statement, the ban, as you indicated in your statement, the ban that exists was really a drafting error that was made in 1938, so the PMA has had a position for some time that the way to correct that is simply to undo that error. We do recognize, however, that that is probably not politically feasible and therefore examined carefully S. 2878, the bill introduced by you and cosponsored by Senator Quayle last year. That we think is an excellent basis for a point of departure.

We think that the safeguards are there, by listing what has come to be called A countries, the ones with sophisticated drug approval systems, the Western European countries and Japan, by listing those and requiring that before any pharmaceutical product be exported to a Third World country, that one of those A countries must have approved it for use by its own citizens.

When that happens, there are a lot of safeguards built into the bill. One of the concerns expressed by critics of the legislation concerns the labeling that occurs in Third World countries. One of the safeguards in your bill, Mr. Chairman, clearly would obviate that because it says that we could export to the Third World only using the same label that is used in the country that approves it, so if it is West Germany, for example, the Federal Republic of Germany, that labeling would have to be used if that were the first approval country, that would have to be used worldwide.

It has the safeguard that the Food and Drug Administration can veto any export to the Third World. That is something that in effect does not exist today because the Food and Drug Administration does not know if our companies are making the drug abroad and exporting it to the Third World, so that is another safeguard built in.

It must not be banned in any of the A countries to be exported, and finally for export to a B-list country or Third World country there would have to be a notice put in the Federal Register so the world would know that it is going to be exported.

Now, added to all of that is the fact that now when drugs are made abroad there is no requirement that the facilities correspond to the GMP or the good manufacturing practices that our companies have built into our plants in the United States. So our view is, given the political realities, that S. 2878 approach is a sound one, it is more restrictive than any approach anywhere in the world. It would be more restrictive, but nevertheless we see that as a very viable political alternative to simply rewriting and correcting the 1938 error.

The **Chairman**. Mr. Swanson, you have a particular interest in this matter. Do you care to comment about that same question?

Mr. **Swanson**. Well, we agree with the approach taken by S. 2878 with the modifications suggested by our colleagues at the PMA. We have made some additional suggestions primarily because of the urgency of our need and the desire to try to address all possible concerns that would delay the speed with which this legislation moves through Congress.

The **Chairman**. Mr. Hart, I referred earlier to a chart that showed some estimates of potential economic impact on the pharmaceutical industry of lifting current drug export restrictions. Some recent discussions with the Congressional Budget Office about these particular data pointed out to me that one missing component of all these analyses is some prediction of the relative impact for smaller firms and in particular they contain no component for biotechnology products. In fact, it may be that for these products, which are really, in the opinion of some, the way of the future, the amount of potential exports which could be obtained may be quite large. Can you comment on that?

Mr. **Hart**. Mr. Chairman, our primary concern, as I mentioned, spoken on behalf of our smaller members which constitute the majority of our association members, is that they be able to take advantage of such a change in policy to try to export their products to generate revenue. As I mentioned, we have international members and so we are especially aware of the aggressive nature through which foreign governments are promoting the acquisition of biotechnology, not just through transfer but through the building of facilities overseas.

According to our information, there are three significant biotechnology companies that have reached agreement to build facilities in the Netherlands and there are two more under discussion.

I note just recently the Italian Government, which is not a listed country I believe under the other proposal, has just allocated 200 billion lira for high-technology development research, of which 20 percent is directed specifically toward biotechnology.

So as I said, Mr. Chairman, as I pointed out, I think our concern is that this policy change not be frustrated to the detriment of our manufacturing base in monoclonal antibodies specifically and the transfer of biotechnology in general.

I think it has been public knowledge since the OTA issues its report and the Department of Commerce as well, that foreign governments are pursuing the transfer of these technologies and their acquisition quite aggressively, and I think that is continuing in pace.

The **Chairman**. Well, thank you so much.

Now let me turn to Senator Quayle, who has taken a great lead in this area and whom I rely on in many ways along with Senator Kennedy and others to help get this legislation passed and carry it through the Congress, who I think has been a good leader in this field. So let me turn to you, Senator Quayle.

Senator **Quayle**. Thank you, Mr. Chairman. I want to first of all thank you for having hearings on this very important subject and thank you for your past, present, and future leadership on this issue. I was fortunate enough to be one of your primary cosponsors on S. 2878 last year and I look forward to working with you again this year as we design legislation on this important subject of drug export reform.

I think it is very important that we do, in fact, get legislation through this year. I think that this is now the beginning of what will probably be a rather long typical legislative process, but I think that the final bottom line ought to be that we ought to get legislation somewhat along the lines that the chairman introduced last year. I think that is certainly where I will be coming from again this year.

I would ask, Mr. Chairman, unanimous consent if I could put in my opening statement.

The **Chairman**. We have already put it in.

Senator **Quayle**. You have put it in. You are way ahead of me, as usual.

I am going to focus with our panel on one area and that is I want to get from you what the two, three, or four major issues of contention are. Maybe you will say that there is only one or maybe there is more than one. I do not want to go beyond four because, you know, you get beyond four and the memory starts fading out. But if we can get three or four major issues of contention that you think are going to be contentious points of discussion through this legislative process, I think it might help us try to crystalize the issue as we begin rather formidable debate on this piece of legislation.

So I will just go down my list here, Mr. Mossinghoff, if you would try to do that first.

Mr. **Mossinghoff**. Thank you, Senator. Senator, the charge made most frequently against legislation of this kind is that it would create some sort of immoral double standard, and it and must be kept in mind, I think, as everyone considers this that the passage or nonpassage of this bill has nothing to do with what drugs are available anywhere in the world. The drugs can be made available there. Most of the members represented on the board of directors of the PMA are of multinational organizations. They have production plants all over the world and they have to make corporate decisions when a drug is first approved to try to recoup the $80 to $100 million investment that has gone into the discovery and development of a drug.

So I think the argument is not a sound one. It has nothing to do with what drugs are available anywhere. And indeed as I pointed out in response to the question of the chairman, that by permitting exports from this country we actually assure a higher standard of quality control and notification of the Food and Drug Administration than otherwise would be the case if the pharmaceutical product was simply manufactured abroad.

I do not think it is a sound argument but it is the the issue most frequently raised by opponents of this very sound legislation.

Senator **Quayle**. So we would advocate that in fact you deal with the export of this drug where you have another "A" country that has a similar process of other industrialized nations, that we would be able then to export that drug to anywhere in the world. Is that basically the starting point?

Mr. **Mossinghoff**. That's right, Senator.

Senator **Quayle**. Now, the other argument is that we should not have—the other extreme argument would be that we should not have anything coming out of this country, we would have an absolute prohibition, continue to have the ban or prohibition of any export unless FDA approves that.

Now, that is one of the issues and I suppose that there are in-between positions on that, but that is one of the major issues, right?

Mr. **Mossinghoff**. That is right, Senator.

Senator **Ouayle**. What is another one? Is that it? Is that all we have to resolve? What I am trying to do, so the other ones might be able to think this thing through, I am trying to figure out what real major issues we are going to have to resolve on that, and then my followup question to that I am going to ask each of you is what we really need to do to get this thing through, because I think—I am with the chairman, I am committed to seeing this legislation passed as he, and so I am going to try to focus if I can and pinpoint as much as I possibly can these areas of disagreement so we will know where the battle lines are going to be drawn.

Mr. **Mossinghoff**. Senator, I might mention another area and that is charges are made, I think based in many cases on old data, about practices in the Third World, particularly practices of, say, the members of the Pharmaceutical Manufacturers Association.

In 1981, we participated very actively in the formulation and publication of a code of conduct through the International Federation of Pharmaceutical Manufacturers Associations, the IFPMA, which is based in Geneva. They have published this code of marketing conduct. All of our member companies of PMA adhere to the code and a mechanism is set up for complaints that might be received from anywhere in the world that some company violated this code of marketing practice or marketing conduct. It may be appropriate for this part of the discussion, Senator, to put that code in the record. It is very succinct, but it is also very comprehensive.

We think we have a good code, our members agree with it, our members are adhering to it, and there is a mechanism in place to police the code through the International Federation.

Senator **Ouayle**. Is there any argument to that?

Mr. **Mossinghoff**. Not that I know of.

Senator **Ouayle**. Again, I want to focus on contentious issues, not ones that we perhaps are going to agree on. I want to look at the points of debate.

Mr. **Mossinghoff**. Well, I think you will find——

Senator **Ouayle**. Is there just one? We have focused on the top one, the licensing process or procedure. Is that——

Mr. **Mossinghoff**. On this one, Senator, I think you will hear allegations that there are dumping practices and illegal or improper or unethical advertising, and so on, and to that my response would be that we do not know of any practices, that everyone has adhered to this code and we believe it is working very well.

Senator QUAYLE. OK. Mr. Sharrock, do you want to add to the points of contention of this legislation?

Mr. SHARROCK. This is a slight variation, but let me describe it because it is a set of words and that is that people sometimes accuse our industry of being in favor of this legislation and say that we favor it even at the risk of patient safety around the world.

I want to assure the committee that patient safety is very much a factor in our minds. We are very much concerned about patient safety, not only in the United States but every place. And I want to assure the committee that this legislation will have no reduction in the protection that is provided to people around the world, because under the current scenario when a company and its experts decides that a product is safe for registration, we then submit that product for registration in several major countries.

As soon as the registration is approved, the product will then be marketed, so we are not talking about whether a product will be marketed, we are really talking about where they will be manufactured. Frankly, the current legislation, as you gentlemen have proposed it in S. 2878, provides a number of safeguards which I won't describe further because they have been described in the testimony, but I do want to assure the committee that there will be no reduction in patient safety anyplace in the world.

Senator QUAYLE. Mr. Swanson, do you want to—I am getting a feeling that the only issue is this licensing process that we are going to have to resolve.

Mr. SWANSON. Let me give you the four issues that I see, Senator. The first one is which country, what are the countries where unapproved drugs may be shipped. In S. 2878 there were two lists and we agree that there should be just one list and that list should be expanded somewhat from the countries included in that bill.

The second issue I think is the status of the drug before it can be exported, does IND have to be on file with the FDA before the drug can be exported or not. If an IND was on file, clearly the FDA had decided that the preclinical studies and toxicology studies permitted the drug to be used in humans in the United States.

The third issue is transshipment, whether or not there can be any provisions in the drug that would prohibit the drug from moving from that country that has approved it. So if country *x* has approved the drug for its own citizens and it is shipped from the United States to that country, is there a prohibition to what that country does with it afterward. We oppose that provision of a prohibition against transshipment.

As we understand it, medicine and medical supplies are exempt from export controls under the current Export Administration Act and we believe that exemption is well considered and there is no reason to change it.

The fourth issue is whether the FDA should review and approve an application for export, and here our major concern is the speed with which that decision gets made. As a small company, we cannot afford long delays in that decisionmaking process.

Senator QUAYLE. OK. Mr. Hart, do you want to add anything?

Mr. HART. Senator Quayle, as I mentioned before, I think you came in, ABC is the new kid on the block on this issue and we represent smaller firms that essentially are involved in research and development biotechnology and product development and many of our members are seeking markets or resources to market their products, so I think it is probably unfair for us to characterize the most contentious points, being a late comer to this process. But our concerns relate more specifically to how an ultimate bill would treat smaller research oriented firms.

I mentioned those two particular concerns in my testimony, that the future markets outside an approved list not be prejudiced unduly at some point in the future. For example, a couple of our member firms have been making some inroads I believe with clinical diagnostics and markets in the People's Republic of China. That is very early now. That is not mentioned in either particular piece of legislation, but we are concerned that either the list becomes too exclusive at some point or the process of seeking markets in the future becomes such a barrier and cumbersome, in and of itself operates as a barrier to smaller firms to try to generate some revenue through sales of products abroad.

Senator **QUAYLE**. In looking at what happened last year, from your perspective what thing really bogged us down in not getting through last year, if you had to pinpoint one thing that really became the final stumbling block in not getting this legislation through?

Mr. **SHARROCK**. Let me ask Mr. Ingram to comment on that. He was actively involved in that testimony last year.

Mr. **INGRAM**. Senator Quayle, I think it was a combination of the time factor, which you have already alluded to, plus some of the issues which Mr. Swanson has identified, the debate over which countries, the FDA rule. I think the countries were the major sticking point last year.

Senator **QUAYLE**. Which countries they could ship to?

Mr. **INGRAM**. Right.

Senator **QUAYLE**. In other words, ship to the country that is approved or ship to anywhere?

Mr. **INGRAM**. Yes.

Senator **QUAYLE**. In other words, that has probably been the main source of contention then, would that be a fair summary? Would anybody disagree with that on this panel?

Mr. **MOSSINGHOFF**. Mr. Chairman, last year at this time I was the Commissioner of Patents and just as an outsider watching this legislative process, I think this legislation might have got lost in the shuffle on the ANDA patent term restoration issue which pretty well occupied this committee and the counterpart committee on the House side, so from my vantage point, I did not see this ever come to any final decision. It was just a matter of other priorities and that was a very active legislative time.

Senator **QUAYLE**. To show a priority from your viewpoint and the industry viewpoint, Congress has a unique way of sometimes expressing what is a high priority and what is a low priority. Would it be helpful for you and the people that are all interested to have this legislation begin down the legislative track as a separate piece of legislation, maybe move it out of the committee here and try to move it through the Senate? Would this be helpful to you from your viewpoint or not?

Mr. **Mossinghoff**. My answer to that I think on behalf of PMA would be very definitely. We think that the issues are well understood, the matter has already passed the House and the Senate at different times, it is recommended by totally non-partisan groups, the Office of Technology Assessment, the National Academy of Engineering. We really believe the time is right for the Congress to act in this area and we would prefer not to see it tied up with other pieces of legislation that might be moving through the process.

Mr. **Sharrock**. We strongly endorse that position.

Senator **Quayle**. Do you strongly endorse that, Mr. Swanson?

Mr. **Swanson**. We endorse it very strongly.

Senator **Quayle**. Mr. Hart.

Mr. **Hart**. Yes, sir.

Senator **Quayle**. OK. Mr. Chairman, I really think that we have got the issues before us. They are not new. You have worked with them tirelessly. I look forward to working with you and trying to get this bill moving and I think that we have got the issues out, we will have them debated, there is obviously going to be some disagreement, but that is not unusual for this committee. And where we can find compromise or whatever it may take, maybe just to have enough votes to move it along. I think last year we almost got it, but this year or by next year we ought to get it. I think it is a major piece of legislation, there has been a lot of work on it, and I reiterate my interest in it and look forward to working with you to move this thing along as much as it takes.

I thank the Chair and thank him for his cooperation and endorsement and sponsorship of this legislation.

The **Chairman**. Thank you, Senator Quayle. We appreciate your efforts.

We want to thank each of you panelists and your associates for being with us this morning. We think you add a lot to this particular hearing. Thank you.

Mr. **Mossinghoff**. Thank you very much.

Mr. **Sharrock**. Thank you.

The **Chairman**. Our next panel consists of Dr. Paulo Machado, of Sao Paolo, Brazil, a former Brazilian Minister of Health; and Mr. C. Payne Lucas, president of Africare, a Washington, DC, based African relief organization. Mr. Lucas is accompanied by Mr. Alan Alemian, Africare project director.

Gentlemen, we are very grateful to have you with us today. We are honored to have you here and, Mr. Machado, we will begin with you.

STATEMENT OF DR. PAULO DE ALMEIDA MACHADO, FORMER MINISTER OF HEALTH OF BRAZIL; AND C. PAYNE LUCAS, EXECUTIVE DIRECTOR, AFRICARE, ACCOMPANIED BY ALAN ALEMIAN, REGIONAL DEVELOPMENT OFFICER, EASTERN AND SOUTHERN REGIONS OF AFRICA

Dr. **Machado**. Mr. Chairman and members of the committee, my name is Paulo de Almeida Machado. I have been a public health physician since 1952. My experience includes working among the most primitive tribes, in the most remote areas of the Amazon region, to being Brazil's Minister of Health from 1974–79.

I will summarize my written statement, respecting your time allowance.

Brazil is a large country, as large as the continental United States, but there is an important ecological difference: The U.S. territory is a broad belt inside the temperate zone between parallels 24 and 49 north, and Brazil extends from 5 degrees north to 34 degrees south. There are different latitudes, different ecosystems, different possibilities for transmission of communicable diseases, different cultural and social conditions.

While in some State capitals they may be performing today a heart transplant and do it successfully, 50 miles away somebody may be dying after a snake bite for the lack of serum. So there is the difficulty of a heterogenous population.

And getting to those differences, it is obvious that Brazil's needs for pharmaceuticals is great. We need a wide variety of pharmaceuticals, different products and different dispensing practices. As far as dispensing is concerned, if we wait for a medical prescription to deliver an antimalaria drug into the remote areas of the Amazon, we may be guilty of murder, while giving without prescription it is possible that some accident will occur, but never a death, and the incidence of malaria is going up 100,000 cases in 1978, 300,000 cases in 1984. The new drugs are needed urgently.

Although difficulties have been already considered today, I still have to remember that we have 10 million infected or exposed to infection by American trypanosomiasis, a disease for which there is no cure at all, 8,000,000 cases of schistosomiasis. All over the world there are 200 million, and we have 8,000,000, and again no effective drug is available.

The list of examples would be very long, therefore we need one specific product. If we need one specific product and it is deemed effective and safe by our health authorities, it is a duty to obtain it from sources willing and capable of selling that product.

One must remember our experience with meningitis. An epidemic was started in 1973 and became serious in 1974 when type A meningococcus was imported from Africa, superimposing to an existing epidemic caused by type C meningococcus which came from the United States; 75,000 cases were reported. Morality was over 10 percent and among the survivors, nobody knows the percentage of handicapped. In Sao Paulo, there were no vacant hospital beds and television reporters escorted children from one hospital to another, looking sometimes not for a bed but merely for a desk on which to place the child.

The only way to control that epidemic was through mass vaccination. Eighty percent of the population of 130 million should be vaccinated as soon as possible with a vaccine that did not exist but had to be created and produced, and we need it right away.

In those days, Brazil did not master the continuous fermentation techniques for the manufacture of vaccines. American manufacturers were contacted but they did not have the approval by the FDA, so we went to France and gave our specifications and French manufacturers have supplied the 100 million doses of vaccines that we needed, actually 110 million. It was a $40 million business. One week after the vaccination the epidemic was over and 2 years afterwards American manufacturers announced that they had the approval by the FDA. I said thank you, gentlemen, but the epidemic is already over.

The meningitis campaign illustrates the advantages of a mature, responsible attitude. How many deaths would have occurred if we had waited for another country's approval? It was our problem, our responsibility and our exclusive interest. We had to make a decision and we did it.

Of course, Brazilian authorities pay attention to decisions taken in other countries approving, restricting or interdicting pharmaceuticals. The FDA is considered a most capable and reliable agency, but it is not geared toward the protection of Brazilian community interests.

Since our 1976 legislation, the administration has only executive capacity and decision is reserved to the National Health Council where the Congress is represented, the universities, leading universities are represented, the industry and, of course, the administration. So it is a broad council with public and wide participation so it is less exposed to errors and to corruption, and this allows us to make our own decisions when a new product comes in and is available.

We need new pharmaceuticals and our needs do not match your needs, and sometimes as a scientist in public health I feel ashamed seeing how many products we have for headache, sleeping pills, or wake up pills and relaxing pills, when millions of people are dying from some diseases in remote countries and there is no scientific research consistently being run for those cases far away. But they are human beings and we need new pharmaceuticals and we need them right now. Good medical treatment is a human right and good medical treatment is not only safe and effective, but in due time, not in the future.

The previous approval by authorities in the exporting country is to be considered as a recommendation but not as a requisite for registration by the Brazilian agency. Some drugs may be approved in other countries and may be rejected in Brazil, and some drugs rejected in other countries and may be accepted in Brazil. Our National Health Council is to decide.

This is briefly my written statement and I stand ready to answer any questions you and your colleagues may have.

Thank you.

[The prepared statement of Dr. Machado follows:]

Statement of
Paulo de Almeida Machado, M.D.
Before the Labor and Human Resources Committee
United States Senate
June 5, 1985

Good morning Mr. Chairman and members of the Committee. My name is Paulo de Almeida Machado. I have been a public health physician since 1952. My experience includes working among the most primitive tribes, in the most remote areas of the Amazon Region, to being Brazil's Minister of Health from 1974-1979.

In my lifetime I have carried lepers in my arms; I delivered children under the light of a kerosene lamp while kneeling on the soil where the mother lay; I suffered the painful experience of burying my patients to whom I was able to offer nothing but my tears and prayers; I have tasted the bitterness of helpless solitude given the absolute lack of minimal resources, and then lead Brazil's brightest medical teams, working in health planning, utilizing stochastic models, simulation models and computers.

For five years, I was the Director of the National Institute for Research in the Amazon and, was full professor at the Catholic University of Campinas. Last year, I had the privilege of being a Visiting Professor at the University of Wisconsin at Madison.

I was a member of the WHO Steering Committee of the Scientific Working Group on Schistosomiasis, for a full 3 year term. I have been a consultant for PAHO on several occasions, and have participated in scientific missions, workshops and symposia in Mexico, Venezuela, Ecuador, Uruguay, Argentina, five countries in the Caribbean, eight U.S. universities, Canada, Portugal, France, Switzerland, USSR, five African countries and China.

I am here today, at the request of your Committee to discuss the peculiarities of the health needs and health laws in Brazil, as these might relate to eventual changes to existing U.S. laws regulating the export of pharmaceuticals.

Brazil is a large country, as large as the continental United States. There is, however, an important ecological difference: the U.S. territory extends east-west, between parallels 24 and 49 north -- a broad belt -- inside the temperate zone. Brazilian territory extends from 5 degrees north to 34 degrees south. So, many different latitudes are responsible for completely different eco-systems and different socio-economic and nutritional conditions affecting our health needs. From the hot and humid rain forest, the Amazon jungle, to the cool southern plains, the savannahs in the Central Plateau, the arid regions in the northeast and the mild mountains in the southeast, Brazil experiences all climates. Today it may snow in the south and temperatures close to 100 F may be recorded in the north. As far as the transmission of communicable diseases is concerned, there to exist the most diverse conditions.

Brazil's population exceeds 130 million. In general, population density is high along the Atlantic coast and very low inland.

The modernization of agriculture and rapid industrial development have induced rapid urban growth and outdistanced the development of education. There are about ten cities where the population is around one million. Sao Paulo exceeds ten million and Rio five million. In all these cities, a fraction of the population enjoys high living conditions and the comforts of modern technology. But there are too many inhabitants still struggling for survival. The huge growth in the gross national product has had little if any impact on social development. As a consequence, urban violence, illiteracy, a high incidence of communicable diseases, poor health care, poor sanitation conditions are still all too common. For economic and cultural reasons, medical professionals are concentrated in the big cities where the very best hospital facilities are located. In several state capitals heart transplants are performed with good results, while 50 miles away there may be someone who cannot get a dose of serum for a deadly snake bite. Urban yellow fever reappeared two weeks ago after 40 years without one single reported case.

Several generations of doctors, including mine, have never seen a single case of yellow fever. But the deterioration of a persistent and efficient control program has been responsible for this recent disaster.

Given its ecological, cultural and socio-economic heterogeneity, it is obvious that Brazil's needs for pharmaceuticals is great. We need more different products and we are forced to allow different dispensing practices. In remote areas where there are no physicians or pharmacies, selling anti-malarial medicines in the absence of a medical prescription may eventually cause accidents. But, waiting for a prescription may lead to death. The incidence of malaria, after years of steady decline, is going up: 100,000 cases in 1978 and 300,000 in 1984. New drugs are needed urgently.

Ten million are infected or exposed to infection by Chagas disease, the American trypanosomiasis. There is no treatment for this disease. There are about 8,000,000 carriers of schistosomiasis. The available treatment is an effective single dose miracle drug. It was widely used and serious complications were eliminated. But our experts discovered that the larval forms are not disturbed by the drug. Adult worms are killed but juvenile forms keep growing and the patient starts passing Schistosoma eggs after 2 or 3 months. Without a new drug, eradication will be impossible.

The list of examples would be very long. Therefore, if we need one specific product and it is deemed effective and safe by our health authorities, it is a duty to obtain it from sources willing and capable of selling that product.

One must remember our experience with meningitis. An epidemic of meningitis started in 1973 and became grave in 1974 when type "A" Meningococcus was imported from Africa. It provoked a new and more dangerous epidemic to the one caused by type "C" Meningococcus, which was brought from the U.S. 75,000 cases were reported. Mortality was over 10% and among the survivors, nobody knows the percentage of handicapped. In Sao Paulo, there were no vacant hospital beds and television reporters escorted children from one hospital to another, looking sometimes not for a bed, but merely for a desk on which to place the child. The only way to control that epidemic was through mass vaccination. Eighty percent of the population needed to be vaccinated as quickly as possible. Eighty million doses of a new vaccine, effective against both types of Meningococcus, were urgently needed. In those days, Brazil did not master the continuous fermentation technique for the manufacture of vaccines and the old existing techniques would not yield the quantity of product as fast as it was needed.

Foreign manufacturers were contacted and vaccines were purchased in France. U.S. manufacturers could not supply it, in spite of being capable of producing it, because the FDA approval would take too long. Actually, when the U.S. industry contacted the Ministry of Health announcing that it had the necessary approval, we had already vaccinated the whole country. In the city of Sao Paulo two million were vaccinated on March 22, 1975, the first day of the campaign. By the 3rd of April hospitals had vacant beds and few new cases were being reported among non-vaccinated newborns.

The meningitis campaign illustrates the advantages of a mature, responsible attitude. How many deaths would have occurred if we had waited for another country's approval? It was our problem, our responsibility and our exclusive interest. We had to make a decision. We did it.

Brazilian authorities pay attention to decisions taken in other countries approving, restricting or interdicting pharmaceuticals. The FDA is considered a most capable and reliable agency; an agency ensuring the best safety to the U.S. people. But the FDA is not geared towards the protection of Brazilian community interests.

In 1946 a decree was issued which stated that no imported pharmaceutical would be registered in Brazil without proof of prior registration in the country of origin. When that decree was issued forty years ago, Brazil had very limited capabilities with which to evaluate safety and efficacy. Several similar decrees were subsequently signed by different Presidents which reaffirmed this policy.

Then for the first time in 1976, this issue was the subject of legislation before the Brazilian Congress. As Minister of Health I was entitled to recommend the issuance of a decree. Instead I chose the long and arduous route of going through our Congress as a form of legitimacy. It was not easy. The government held a small majority, but it was a lethargic one, as usual, when the President is powerful. The opposition was pugnacious and alert. The Health Committee was controlled by the opposition and their members were up to date with health problems. It was known they would not approve the legislation without first discussing it to the last comma. I had to testify before seven three hour sessions of the Committee. After convocation by the Congress, I was questioned for eight consecutive hours before the House of Representatives. Finally, the law was approved and for the first time Brazil had comprehensive norms for the health sector, including pharmaceuticals.

At that time the public was disturbed by publications appearing in the U.S., and widely distributed in developing countries, accusing multinational corporations of poisoning our children, draining our resources, and using our people as guinea pigs. Thus it was impossible to change the old requirement of the prior approval in the country of origin even though Brazil was already capable of testing the effectiveness and safety of most drugs. Political not technical reasons prevailed. No technical reason would have successfully opposed emotional arguments.

According to the 1976 law, while approval in the country of origin is required, it is not enough. A product approved by competent authorities in another country may be rejected by the Ministry of Health. Restrictions and even prohibitions issued in other countries will be analyzed in my country and our authorities will make their own decision. Genetic, socio-economic, cultural and administrative structures are to be considered in addition to the routine scientific procedures.

Since 1976, according to the law, the DIMED, the Ministry of Health's drugs division, is the executive agency and the National Health Council is the decision center. The Council is supported by technical committees. Representation of universities, professional associations and industry is also required. Following enactment of the law, the Minister of Health no longer has full powers to decide by himself on the approval or rejection of pharmaceuticals.

Therefore, since 1976, we have a reliable collegium including the National Institute for Health Quality Control plus capable scientific centers at different universities, entitled to choose the best alternatives as far as the community's needs are concerned.

We need new pharmaceuticals and our needs do not match your needs. We have serious human ailments to be cured today. Other countries do not have the very same problems.

We are in a hurry. Other countries may not evaluate such an urgency.

Getting appropriate treatment is a human right. Appropriate means not only safe and effective, it also means early treatment.

Deep changes are occurring in Brazil. A new Constitution will be voted on soon, many laws and decrees were and will be changed. Our current norms may be updated and national capability may be recognized.

The previous approval by authorities in the exporting country is to be considered as a recommendation but not as a requisite for registration by the Brazilian agency.

All my statements are personal, they do not intend to reflect official opinions or trends. I hope my testimony has been of help to your committee in its deliberations.

I stand ready to answer any questions you and your colleagues may have.

The **Chairman**. Thank you, Mr. Machado. I read your written statement and it is very touching and I think you make some very good points on behalf of countries all over the world who can use the assistance of this bill.

Mr. Lucas, I wonder if I could impose upon you to accommodate one of our witnesses who really needs to catch a plane at 12:30? I understand he will only take 5 to 10 minutes, and that is Mr. Humphrey Taylor, president of Lou Harris & Associates, out of New York. If we could allow him to come and make his statement at this point and accommodate him, I would appreciate it.

Welcome to the committee, Mr. Taylor. We are glad to have you here and we hope that you will be able to catch your plane.

STATEMENT OF HUMPHREY TAYLOR, PRESIDENT, LOUIS HARRIS & ASSOCIATES, INC.

Mr. **Taylor**. Thank you very much, Mr. Chairman and Senator Kennedy. I am very honored to be asked to be here today to testify on this bill.

I have a written statement which I will summarize for you, if I may.

The **Chairman**. We will place the written statement in the record.

Mr. **Taylor**. I would like to start by explaining that I am not here to support or oppose the bill, and that indeed I know very little about it or the arguments for or against it. The reason I was asked to come here today relates to the possibility that the marketing practices of the drug companies and their agents in the Third World might be monitored and audited to determine whether or not these marketing practices were in compliance with an agreed code of conduct or set of standards, either one that exists now or one that might be devised in the future.

Based on our experience, which I will describe to you briefly, I have no doubt that it would be possible to conduct such an audit on a regular basis in selected third world countries. An audit of this kind could check the marketing practices of selected drug companies or of selected categories of drugs, in relation to any kind of activity which is visible to third parties. That is to say, it is possible to check what drugs are available, how they are made available and distributed, how they are labeled and described in the marketing and supporting literature, and how they are promoted and advertised.

What cannot be checked reliably are transactions which take place in private. Private conversations between salesmen and Government officials or physicians would fall in this category, as would sales commissions and the possibility of corrupt financial practices.

The reason that we at Louis Harris & Associates are competent to talk on this subject is that we have been conducting a somewhat similar piece of research for the last 7 years for the infant formula industry. For 6 years, ending in 1983, we conducted an annual audit of the marketing practices of infant formula companies in selected third world countries for Bristol-Myers, whose subsidiary, Mead Johnson, is one of the three large U.S. manufacturers of infant formula.

In 1984, for the first time, this inuiry was broadened and cosponsored not only by Bristol-Myers, but also by Abbott Laboratories and Wyeth Laboratories, the two other major U.S. manufacturers of breast milk substitutes.

In the earlier investigations we sought to monitor the compliance or noncompliance of Bristol-Myers employees and their agents with their own code of conduct. In the 1984 study, we sought to monitor the compliance of the three companies with the WHO code relating to infant formula marketing practices.

Very briefly, let me describe what we do: The objective of the 1984 study was to monitor the marketing practices of the three companies in relation to the following areas:

First, to establish whether there is any media advertising or other promotion of infant formula aimed at the general public (that is forbidden by the code);

Second, to investigate the incidence of advertising or promotion of infant formula to mothers in hospitals or physicians' offices (which is also forbidden);

Third, to find out if the companies are making direct contact with mothers via mothercraft nurse services or other representative activity;

Fourth, to assess compliance with the labeling requirements of the code; and

Fifth, to inquire into sampling practice via samples or discharge packs provided directly to mothers through hospitals or clinics or private physicians.

The 1984 study was conducted in 13 countries in the Caribbean, in Central and South America, in Africa, the Pacific and Asia, which are listed in my paper.

My statement describes the detail and the methodology in more detail. I will not bore you with that now. I have a copy of the full report of that study which I would be happy to make available to you which show the results of that.

The CHAIRMAN. We would be delighted to have that.

Mr. TAYLOR. Turning if I may from infant formula to what might be done in relation to the marketing of pharmaceutical products and ethical drugs, I believe it would be a relatively simple matter to check the following for any given list of drugs or drug categories:

First, what drugs are or are not available through pharmacists and possibly through doctors' offices or hospitals?

Second, how are these products labeled? And what information is and is not included in the labeling, packaging and supporting documentation?

Third, what information is or is not provided relating to side effects?

Fourth, is the expiry dates printed on the drugs for sale and how do these compare with the dates of purchase?

Fifth, the prices of these products?

Six, what products are available legally without a doctor's prescription, and which ones can only be obtained legally with a prescription?

Seven, which products should only be obtainable with a doctor's prescription, but can actually be purchased without a prescription;

something I understand is a common practice in quite a few third world countries?

Eighth, how are these products promoted and advertised to physicians, health care professionals and government agencies?

If the legislation which you are considering were to include some kind of code of conduct relating to the marketing practices of drug companies, then I am confident that these aspects of the code which are open to public view could be monitored quite easily and quite inexpensively.

Thank you.

[The prepared statement of Mr. Taylor follows:]

LOUIS HARRIS AND ASSOCIATES, INC.

TESTIMONY BY HUMPHREY TAYLOR, PRESIDENT OF LOUIS HARRIS AND ASSOCIATES, INC. BEFORE SENATE LABOR & HUMAN RESOURCES COMMITTEE

JUNE 5, 1985

Mr. Chairman, Senators, I am honored to be asked to come here today to testify on this bill.

I should start by explaining that I am not here to support or oppose the bill, and that indeed I know very little about it or about the merits or demerits of the bill. I hold no brief for or against it, nor have any of our clients (some of whom are in the drug industry) ever discussed the bill with me or my colleagues.

The reason you asked me to come here today, I believe, relates to the possibility that the marketing practices of the drug companies and their agents in the Third World might be monitored and audited to determine whether or not these marketing practices were in compliance with an agreed code of conduct or set of standards.

Based on our experience, which I will describe to you in a moment, I have no doubt in stating that it would be possible to conduct such an audit on a regular basis in selected Third World countries. An audit of this kind could check the marketing practices of selected drug companies or of selected categories of drugs, in relation to any kind of activity which is visible to third parties. That is to say, it is possible to check what drugs are available, how they are made available and distributed, how they are labeled and described in the marketing and supporting literature, and how they are promoted and advertised.

What cannot be checked reliably are transactions which take place in private. Private conversations between salesmen and government officials or physicians would fall in this category, as would sales commissions and the possibility of corrupt financial practices.

The reason that Louis Harris and Associates is competent to talk on this subject is that we have been conducting somewhat similar research for the last seven years for the infant formula industry. For six years, ending in 1983, we conducted an annual audit of the marketing practices of infant formula companies in selected Third World countries for Bristol-Myers, whose subsidiary, Mead Johnson, is one of the three large U.S. manufacturers of infant formula.

In 1984, for the first time, this inquiry was co-sponsored not only by Bristol-Myers, but also by Abbott Laboratories and Wyeth Laboratories, the two other major U.S. manufacturers of breast milk substitutes.

In the earlier investigations we sought to monitor the compliance (or non-compliance) of Bristol-Myers employees and their agents with the Bristol-Myers code of conduct. In the 1984 study we sought to monitor the compliance of the three companies with the W.H.O. Code relating to infant formula marketing practices.

The 1984 Study in Detail

The objective of this inquiry was to monitor the marketing practices of three companies involved in the sale and distribution of infant formula used as breastmilk substitutes in developing countries.

The basic areas of inquiry were as follows:

(1) To establish whether there is any advertising or promotion of infant formula aimed at the general public (this is forbidden by the Code).

(2) To investigate the incidence of advertising or promotion of infant formula to mothers in hospitals or physicians' offices (also forbidden).

(3) To find out if the companies are making direct contact with mothers via mothercraft nurse services or other representative activity (also forbidden).

(4) To assess compliance with the labeling requirements of the Code.

(5) To inquire into sampling practice via samples or discharge packs directly to mothers and through the hospital/clinic or private physician. The practice of providing free supplies for institutional use was also examined.

Countries Covered

The 1984 investigation was conducted in the following 13 countries.

- Dominican Republic
- Ecuador
- Haiti
- Indonesia
- Jamaica
- Kuwait
- Malaysia
- Mexico
- Nigeria
- Pakistan
- Philippines
- Thailand
- Venezuela

The intention of the inquiry was to report in detail the precise activities observed, not to comment on whether these activities should be considered as infringements of the W.H.O. Code. This is particularly relevant in the context of product labeling, where manufacturers have often interpreted W.H.O. requirements in different ways.

Time Scale

It was also the intention that 1984 inquiries should relate only to activities recorded after July 1, 1984, the date by which the three companies sought to be in compliance with the W.H.O. Code.

The inquiry was conducted between August and October 1984.

The Inquiry in More Detail

Investigations were carried out in the main commercial center and in one or more towns or rural areas in each country as a general index of marketing activity in that country. The inquiry was structured on the following basic areas:

(1) Advertising and promotion aimed at the general public

A thorough search was conducted of the mass media (press, radio, television) for evidence of advertising of infant formula. A search was also made for evidence of outdoor advertising and point-of-sale activity in retail outlets. Additionally, interviews were conducted with media representatives, advertising agencies, and in some cases, advertising monitoring services.

(2) Promotional activity in hospitals and physicans' offices

Our investigators visited hospital maternity departments and the offices of physicians involved in baby care, in order to check for the presence of any promotional material aimed at mothers. They specifically looked for posters, leaflets, brochures or booklets (including educational material provided by the companies). They also recorded instances where infant formula was visibly displayed.

In order to carry out this search, investigators in each country were required to visit eight hospitals/clinics with sizable maternity departments. The instruction was that five hospital maternity departments should be in the main commercial center. The other three hospital maternity departments were to be outside the main city -- in smaller towns/rural areas. Where applicable, hospitals were selected to cover both the public and private sectors.

As regards primary care physicians, investigators were instructed to visit ten physicians' offices -- with an even balance between those inside vs. outside the main city. The physicians concerned were primarily those involved in baby care -- i.e., pediatricians, obstetricians/gynecologists, general practitioners.

When visiting these hospitals and offices, investigators made their own visual search for promotional material. Wherever possible they also sought to obtain further information by conducting interviews with members of staff. Most commonly these interviews were conducted with nurses or receptionist/secretarial staff, although in some cases physicians themselves were interviewed.

(3) Mothercraft nurse/rep. contact with mothers

Investigators in each country sought to obtain this information directly from the companies involved in the sale and distribution of infant formula. The aim was to establish whether any of these companies operate a mothercraft nurse service -- or conduct other representative activity which involves direct contact with mothers. Companies operating services of this type were asked to define the precise duties of their mothercraft nurses or representatives. In order to obtain this information, investigators approached personnel at management level.

(4) Product labeling

At least five retail outlets involved in the sale of infant formula were visited in each country -- all of them generally in the main city studied. The purpose of these visits was to scrutinize the labeling of the available brands of formula. Investigators recorded the extent to which these brands complied with ten requirements of the W.H.O. Code. The following are what their labeling should include:

a) The words "Important Notice" or equivalent.

b) The expiry date by which the product should be consumed.

c) The ingredients used.

d) The composition/analysis of the product.

e) The storage conditions required.

f) A statement that the product should be used only on the advice of a health worker.

g) A notice to the effect that breastfeeding is better than the use of manufactured infant formula.

h) Instructions for proper preparation.

i) A warning about the dangers of mixing formula incorrectly.

j) No pictures of infants. However, graphics may be allowed for easy identification of the product as a breastmilk substitute and for illustrating methods of preparation.

Investigators were also required to check that all the necessary information was provided in the main local language, and to ensure that it was clear and easily readable.

Any possible labeling irregularities were recorded. However, it must be pointed out that labeling irregularities are sometimes difficult to define. For example, the warning as to dangers of incorrect mixing is expressed in different ways on different brands, and with varying degrees of detail.

(5) Sampling

The possible use of direct sampling to mothers was assessed in a number of ways:

- Investigators' own observation at hospitals and physicians' offices.
- Information provided by staff interviewed at these locations.
- Information given by management staff at the companies/ distributors with whom interviews were achieved.

The same sources were used to establish whether there was any distribution of discharge or sample size packs to mothers leaving the hospital.

Information was also sought from the above sources on sampling to individual physicians. Where possible, investigators sought to ascertain the frequency with which physicians received samples, the quantities they received, and the extent to which these were solicited, or provided unsolicited.

As far as possible, full details were obtained as regards the location and nature of any promotional material. Where feasible, photographs or examples of such material were obtained.

I should stress that -- unlike most of the research the Harris firm conducts -- this inquiry was not based on scientific sampling, nor are the results in each country projectable to the nation as a whole.

What we sought to do was to investigate a reasonable number of hospitals, clinics and doctors' offices in two or more locations in each country to determine if there was any evidence of possible violations of the W.H.O. Code. This amounts to a spot-check conducted at places of our choosing. The three companies were not consulted about the selection process; nor were they aware of the choices made until they received our report.

The report of our findings was provided to the three companies earlier this year. They have now shared our report with a number of their critics -- in particular, the church groups and watchdog organizations which have taken a particular interest in the issue of infant formula marketing. Some of the organizations had been briefed by our three corporate clients in advance of the study and had been given the opportunity to suggest changes in our investigators' instructions and particular hospitals or clinics to be checked.

What Might Be Done to Audit the Marketing of Prescription Drugs

So much for infant formula. What would it be possible to do in relation to the marketing of pharmaceutical products and ethical drugs? It would seem to me that it would be a relatively simple matter to check the following, for any given list of drugs or drug categories:

1) What drugs are or are not available through pharmacists and possibly through doctors' offices or hospitals?

2) How are these products labeled? And what information is and is not included in the labeling, packaging and supporting documentation?

3) What information is or is not provided relating to side effects?

4) The expiry dates printed on the drugs for sale and how these compare with the dates of purchase?

5) The prices of these products?

6) Which products are available legally without a doctor's prescription, and which ones can only be obtained legally with a prescription?

7) Which products should only be obtainable with a doctor's prescription, but can actually be purchased without a prescription?

8) How these products are promoted and advertised to physicians, health care professionals and government agencies?

If the legislation which you are considering were to include some kind of code of conduct relating to the marketing practices of drug companies in Third World countries, then I am confident that those aspects of the code which are open to public view in this way could be monitored quite easily and inexpensively.

Thank you very much.

The **Chairman**. Thank you so much, Mr. Taylor. We will let you go so that you can catch your plane. You are going to barely make it.

Mr. **Taylor**. Thank you.

The **Chairman**. We appreciate your appearing before the committee.

Senator **Kennedy**. Mr. Taylor, we want to thank you. If the decision is made about some kind of review, we hope that we will be able to draw on you and your suggestions about how that might be structured.

Mr. **Taylor**. We would be very delighted to help in any way we can.

Senator **Kennedy**. Thank you very much.

The **Chairman**. Thank you so much.

Let's now turn to Mr. Lucas, and we apologize for doing that but, as you can see, he is going to barely make his plane.

Thank you, Mr. Lucas.

Mr. **Lucas**. Mr. Chairman and members of the committee, Africare is pleased to have this opportunity to provide testimony on the subject of the changes being proposed by you to amend the Federal Food, Drug, and Cosmetic Act as regards conditions governing export of U.S. manufactured drugs to other countries.

Africare has not had the opportunity to review recent drafts, if any, of proposed legislation by you. We, however, reviewed S. 2878 introduced in July of 1984 and we understand that even with modifications now being considered, the bill will attempt to revise those aspects of existing legislation which discourage U.S. manufacturers from producing in the United States medicines which, although deemed acceptable by other national regulatory agencies, have not been approved by the U.S. Food and Drug Administration.

We realize that this is a complex issue. However, we believe that all parties wish to accomplish what is in the best interests of people who need and use medicines, particularly in the developing regions of the world where we work. It is from our perspective as a development assistance organization that we comment and offer our insights.

Africare is a private, nonprofit development assistance organization founded in 1971 to improve the quality of life in rural Africa. It has worked closely over the past 14 years with more than 20 Sub-Saharan governments in programs of health, food production, water resources development, relief and refugee assistance.

Our work in health has brought us into health care at all levels—in the villages, in the training of health workers, in the planning of national level primary health care efforts, and in programs to improve management and distribution of pharmaceuticals through government-operated health facilities. It has involved us in the mainstream of discussion and thought in Africa on international health matters.

The countries where we work, unlike the United States, have not reached that point in their development where they can focus their health resources on programs for the elderly, or on research into cures for cancer, heart disease or illnesses and injuries generally associated with the way and standard of American living.

In Africa and in most of the developing world, people are concerned with survival to the age of five. They often have a life expectancy of no greater than 40 years. They live in environments much harsher than many Americans can imagine.

It is only recently, with the tragedy being experienced in Ethiopia and other regions of Africa, that many Americans have come to appreciate the unusually high standard of living we enjoy, and to respect our neighbors on other continents for the hardships that they must endure.

In countries where we work, malnutrition is the largest single general cause of poor health. Diseases such as malaria, schistosomiasis, river blindness, guinea work, hookworm, diarrheas of many origins, and respiratory tract infections, to name a few, are found in large numbers of the populations. These diseases take a serious toll on the people.

When we hear statistics on the number of people worldwide, for example, affected by schistosomiasis—200 million—and when we learn the debilitating impact of that and other tropical diseases, we can understand why developing countries insist that pharmaceutical companies take a greater role in developing tropical cures. Cures involve not simply discovering medicines, but making them available in forms which can enable broad distribution, for which patient compliance is feasible even with rural and nonliterate populations. These are conditions we do not face very often in the United States.

A breakthrough for treating schistosomiasis, the drug praziquantel, was discovered not too long ago by Bayer AG of West Germany, a pharmaceutical firm with a long history of research and development of tropical medicines.

Praziquantel is a developing country's ideal type of medicine in that it addresses a medical problem which causes high rates of morbidity and mortality in large numbers of the population, and which detracts from the productivity of the country. It is economical to purchase and administer, it is highly effective with cure rates approaching 95 percent for all forms of schistosomiasis, and it is simple to administer in that all that is needed is a 1-day course treatment in tablet form.

That Bayer was the company to discover this cure is not unusual, however, something is to be learned from the experience. Praziquantel was first discovered in 1972, but only by 1980 did Bayer obtain approval from the regulatory body in West Germany for its marketing and sale. To demonstrate its efficacy and safety, Bayer had to conduct trials in populations where schitosomiasis was found. Therefore it obtained permission to manufacture and export the drug for trial applications.

Following approval in West Germany, the United States subsidiary of Bayer, Miles Laboratories, in July 1980, applied for and received approval to study the use of the drug in humans in the United States, in immigrant populations from Southeast Asia having schistosomiasis. By December of 1981, Miles submitted its findings to FDA, and withih a year, by December 1982, Miles received FDA approval for the manufacture and sales of the drug both in the United States and for export.

The rapid processing and approval of the Miles application is unusual, since depending upon how the FDA regulations are read, this instead could have been a very extended process. With the case of praziquantel there was very strong cooperation and there was understanding, review by an individual in FDA who himself had once practices medicine in Africa. Also, the U.S. Agency for International Development had urged Miles Laboratories to apply for FDA approval, since AID wished to use the drug in programs it was supporting, and it needed FDA approval before it could purchase the drug.

The drug under current regulations could not have been manufactured for sale to AID by U.S. pharmaceutical manufacturers until it received FDA approval. Fortunately, that process was short. In general, however, it appeared that U.S. manufacturers are reluctant to devote resources needed to the piloting and producing new drugs for tropical diseases because of the extended periods they expect they will have to wait, and because of the difficulties they will incur in testing the drug, since in many instances there is not an adequate size population group in the United States having the tropical disease in which trials can be conducted.

In the 20 countries where Africare works and has programs, our approach has always been to provide decisionmakers with the support and counsel they request to solve their problems. The health picture in many parts of Africa is difficult, and the choices a government must make are equally trying. Resources are limited and choices must be made on how to best apply them.

Yet it is the decisionmakers in those countries that, when provided adequate information and guidance, are in the best position to weigh the various alternatives and choose the best solutions. If a country in Africa has been provided the results of an approval by the West German regulatory agency on a drug such as praziquantel, if the drug has been shown to have met the necessary standards of efficacy and relative safety, and if the drug has been approved by the developing country for import, then it would seem counterproductive for a U.S. regulatory agency to prohibit U.S. manufacturers from producing the drug for sale to that country.

Africare, in its many years of working with host governments in Africa, has been impressed by the increased number of medical and health professionals whose expertise enables them to make these types of decisions. We believe that it would be presumptive and patronizing for a regulatory body in the United States to intervene between the manufacturing firms and countries in need as regard the sale of such proven medicines.

Africare in its work has constantly urged, and at times challenged, the pharmaceutical industry to increase its resources to bring to bear on providing preventive and curative medicines. Therefore, we urge this committee to determine what progress can be achieved along the lines proposed by Senator Hatch to revise legislation in a way which can promote increased U.S. development and supply of efficacious and safe medicines.

The present legislation, which places the Food and Drug Administration in the position of the sole agency to review determine acceptability for exports, fails to take into account that other developed countries have suitable criteria and agencies for reviewing and determining the safety of drugs. It also fails to recognize that each developing country must and should be in a position to weigh and evaluate its needs and determine how they should be met.

Countries in Africa faced with high levels of morbidity and mortality in entire rural populations because of malaria, schistosomiasis, diarrheas, respiratory illnesses, and other diseases, experience great drain on their most precious resources, the human potential. These countries are unable to develop large sections of their rural areas because rural populations cannot be maximally productive. The solutions are not easy, since medicines alone will not break the cycle of disease and poverty. There continues to be a strong need for health education. One thing that most health care practitioners will attest to, however, is that unless you can treat the sick person for the disease he has, you will have difficulty in gaining his confidence and teaching him how to prevent it.

As one specific step toward a better understanding of the issues at stake, Africare recommends that this committee make fuller use of third country testimony on this subject. It would be relatively simple to identify objective and qualified experts from countries in Africa and from other regions to discuss the relative merits and demerits of the arguments being presented.

In a country as small as The Gambia, for example, the government in 1984 passed a National Medicines Act which was drafted with World Health Organization assistance. The implementation of that act is entrusted to a national medicines board comprised of a chairman and nine other professionals. The act establishes a system for reviewing and evaluating the drugs that the Government wishes to import for its use, and it has established a mechanism for regulating private sector imports and sale of pharmaceuticals. The act is being recommended by WHO as a model to be considered by other countries.

The Gambia is not an exception. There are other developing countries with equal levels of expertise and organizations to deal with these matters, and this committee in its deliberations should give full attention to the views of those parties in determining its position.

Thank you, and we would be happy to answer any questions.

The CHAIRMAN. Thank you, Mr. Lucas. I want to thank you and Dr. Machado for being here. I want to especially express my deep appreciation to you, Dr. Machado, and that of the committee for your testimony and your willingness to take the time to travel this long distance to testify here today on this very important issue. Your testimony has touched me and I just want you to know that that is very important.

Mr. Lucas, I have been impressed with your testimony as well.

Mr. Lucas, I do have one question I would like to ask your associate, Mr. Alemian, and that is, sir, in your experience have any of the African nations recently considered imposing a requirement that all imported drugs must be approved in the exporting country?

Mr. ALEMIAN. Well, the most recent exposure I had to that question was in a workshop that was sponsored by the World Health Organization in Banjol, in The Gambia, and in that setting they had medical care and pharmacists and health specialists from about 10 neighboring countries. There were about 30 participants. A topic came up under discussion during a session where they were reviewing the National Medicines Act of The Gambia.

The position that The Gambia has taken is as follows, that they will consider a drug regardless of the country of manufacture and whether or not it has met the regulatory agency standards of the country of manufacture, provided it has been approved for marketing and sale in another country whose review standards they recognize. That would be too say in the case of—let us use praziquantel as an example. If it had been approved in West Germany and it were manufactured in the United States but not yet approved by the FDA, it still would be considered for purchase and import by The Gambia Government. They have a National Medicines Board which reviews such matters.

I should add, in addition they have a national formulary, so their starting point is an approved list of drugs in stated dosage forms and strengths. That is a starting point, and then to add anything else requires review by the National Medicines Board.

The CHAIRMAN. Thank you. If you can provide for the record your analysis of that, plus your analysis of the type of leadership and the controversies and the politics involved and some of the things that are going on in Third World countries, I would appreciate that as well and we will include that in the record.

Mr. ALEMINAN. Thank you.

The Chairman. I want to thank all three of you for being here. It has meant a lot to the committee and has been very helpful to us and we appreciate your being here.

Senator Dodd, I am sorry.

Senator DODD. Let me just apologize, if I may, to you and to the witnesses that have been here this morning. We had a hearing that went on for 3 hours right down the hall, in fact, and I did not get a chance to get down here earlier.

I did have a chance, Dr. Machado, to read your testimony and it is moving testimony and it is a gracious thing to come this far. Mr. Chairman, I congratulate you on the holding of the hearings and I am confident, as I think you are, that this is a problem that we will be able to hopefully resolve in a constructive way and do so with some degree of dispatch because it is a pressing issue not only for obviously for industry in this country but frankly, more importantly in many ways, for people who count on the quality of pharmaceuticals that are produced in this country that may not reach the standard that we would require of them but certainly have proven their efficacy in corners all around the globe.

I happen to have traveled, doctor, in all of the Amazon region. I went down the Amazon River in a 15-foot boat some 20 years ago from Laticia, Colombia, to Manaus and from Manaus down to Porto Velho on the Medeira and saw a good part of that world and there are not physicians and clinics and doctors out there and I know that some of the medicinal supplies that we can provide would spell the difference between life and death, very simply, for diseases that we would long since have forgotten about in this country.

So I mention again, Mr. Chairman, my apologies to all of you for not being here earlier.

The Chairman. I appreciate that, Senator, and certainly we look forward to your help on this matter because you understand a lot of these issues and you can be of inestimable help in the ultimate resolution of any conflicts or problems we have. Thank you again, very much.

Our final panel will be one person, Dr. Sidney Wolfe, director of the Health Research Group of the consumer organization Public Citizen's Health Research Group—two people, I am sorry, Dr. Wolfe and Nancy Drabble of Congress Watch. I would like to thank both of you for joining us today and welcome you to the committee again, Dr. Wolfe and Ms. Drabble. You are regular participants before our committee and other committees in the Congress and we appreciate your taking time to be with us today and we will appreciate it if you could summarize. I do not mean to press you on summarization, but I have got to leave in just a few minutes and I do not want to leave. I would like to listen to you and hear what you have to say, so if you could summarize then maybe we could have some questions and draw a lot of matters out that way.

Dr. WOLFE.

STATEMENT OF DR. SIDNEY M. WOLFE, DIRECTOR, PUBLIC CITIZEN'S HEALTH RESEARCH GROUP; AND NANCY DRABBLE, DIRECTOR, PUBLIC CITIZEN'S CONGRESS WATCH

Dr. WOLFE. Thank you. Public Citizen vigorously opposes any legislation that would allow American drug companies to manufacture and export to international consumers any drugs which have not been found by our Food and Drug Administration to be acceptable for sale to American consumers. We opposed S. 2878 introduced in the 98th Congress and we find that the draft legislation dated December 1984 circulated by Genentech shares the flaws of S. 2878.

We have attached to our testimony—and I will not read it—a list of 19 health, consumer, international, religious, and labor organizations which are not involved in or invited to these hearings that also oppose allowing exports of unapproved drugs.

I would like to add that amongst them are the International Chemical Workers which represent not 25 workers, as does the Dow group that is in favor of this legislation, but they represent 5,600 workers who are opposed to the legislation, despite what we and they believe to be a relatively small number of jobs that might be created.

We also submit for the record a package of some of the many letters we have received from foreign doctors, health professionals, and organizations all over the world opposing the export of unapproved drugs and, with your permission, I would like that to be attached to the record with our other testimony.

The Chairman. Without objection, your full statement and those matters will be placed in the record as well.

Dr. WOLFE. We have just received a telegram 2 days ago from an international organization called Health Action International which is associated with the International Organization of Consumers Unions, which is, as it says, an international organization that includes Consumers Union in this country and counterpart organizations all over the world. I would like to just read you this telegram:

"Participants at Health Action International on the 2d of June"—i.e., this last week—in a meeting at Iserlohn, West Germany, strongly condemn efforts to allow the export of FDA unapproved drugs from the United States. The 62 participants from 17 countries in Europe, North and Latin America, Africa and Asia are shocked that the United States should be contemplating such a retrogressive step. We strongly oppose any U.S. move to derestrict drug exports because:

> 1. It would run directly counter to the growing tide of professional, medical and consumer opinion which sees an urgent need to rationalize drug use.
> 2. It should greatly increase the likelihood of inessential, irrational and harmful drugs being marketed in developing countries.
> 3. It would stand in stark contrast to vigorous FDA controls on the home market which have long been a model for other countries.
> 4. We urge members of the United States Congress and the Senate to join in opposing any bill which would deny citizens of other countries the protection that U.S. citizens have come to expect.

We have also had a communication this week from the world renowned British pharmacologist and physician at Charing Cross Hospital in London, Dr. Andrew Herxheimer, who is the editor of the Drug and Therapeutics Bulletin, which is something like the Medical Letter in this country, except that, unlike the Medical Letter, the British Government sends it free to every physician in Britain. I think that, in itself, would be a good model for this country. Dr. Herxheimer has the following statement:

> I am the editor of a long established independent drug bulletin for prescribers, published in England and distributed in translation throughout Latin America, and the chairman of a new association of editors of drug bulletins around the world. The proposals to permit the export of unapproved drugs from the U.S. fill me with dismay. The drug regulatory system in most developing countries is too weak to keep out ineffective or hazardous drugs, as is recognized by a compromise proposal to restrict exports of unapproved drugs to countries with well-constituted drug authority such as the Federal Republic of Germany.
>
> However, any drug could be promptly re-exported to any other country, thus defeating the objective of the restrictions. Doctors in Third World countries are starved of independent information about medicines and get most of their information from the pharmaceutical companies. They will not be able to resist the powerful sales effort. Perhaps even worse is the fact that most drugs, which in the U.S. and other developed countries are dispensed only on prescription, can be freely bought over the counter in developing countries. Acceptance of the provision to permit the export of unapproved drugs would seriously damage the health in developing countries.

Now, on this whole question of re-export, I would fully agree, based on some conversations I have had, with what Mr. Scarlett and Dr. Young said this morning, namely that there is no way of policing the re-export or transshipment as it is called of pharmaceuticals. There may be some controls which may work, as Senator Kennedy pointed out, in the military sphere, but I have spoken to two different people in both Geneva and in the European section in Denmark of the World Health Organization and they both agree that it would not be possible to police that. I have also spoken to someone who has contacted a number of people in American pharmaceutical companies who also agree that it would not be possible to police that.

That is not to say that even if, theoretically, no re-export would occur, that it would still be tolerable to have export to so-called western countries with adequate drug regulatory systems.

Senator **Kennedy**. Did not WHO last year though have a different position?

Dr. **Wolfe**. On the re-export question? Well, last year the bill that was——

Senator **Kennedy**. Just on the legislation generally and on the——

Dr. **Wolfe**. Dr. Dunn last year said that in certain circumstances, and he quoted the—he was referring specifically to the tropical disease examples—that the World Health Organization would not want to restrict the flow of those kinds of drugs. However, I think the bulk of opinion within the World Health Organization is not to support this legislation. In fact, in response to letters that they received from other people, including one from me, they said that Dr. Dunn's testimony was not meant as an endorsement of this legislation but, rather, that some way should be worked out to get drugs for diseases that do not exist in the United States, and I think there is a way. You just heard one example of it before.

But I think that the whole question of re-export is a real serious one and I hope that other people could be polled to see whether they agree with the FDA at least for drugs as opposed to perhaps military things, there is not any way to police that, and that in fact we would be doing the equivalent of shipping all over the world drugs that really are not approved here.

I would just like to make a couple of other points and then Ms. Drabble will make some comments on the legislation. Senator Metzenbaum alluded before to the examples of six drugs which were approved in the United Kingdom all in the last few years but later banned because they were dangerous. Between the six drugs, there were somewhere between 50 and 100 deaths and 15,000 adverse reactions. None of these drugs was approved in the United States. Most, if not all of them, were pending approval but had not met U.S. standards.

I think the question that the PMA raises is a perfectly legitimate one. The issue is not specifically are people in some of these countries going to get the drugs, but the question is if people die in the United Kingdom or other Western European countries from drugs that were not approved here, are the drugs going to be made in the United States with the "Made in U.S.A." label, or are they going to be made somewhere else. That is the question, and the reason for opposing even the export to the so-called western countries is so that if those deaths occur, as unfortunately they do regularly, from drugs not approved here but approved in western countries, we do not want to be responsible for manufacturing them on this soil. Unfortunately, there is nothing we can do about their being made in other countries. We do not have control over that, just as we do not have control over the re-export.

Just one other comment on the so-called tropical disease issue. The drug that I had as an example in my testimony is the same one that Mr. Lucas just alluded to, praziquantel. I think the point that I would make in a couple sentences is that even if there are tropical disease type drugs which must be given special consideration due to different public health import of these diseases in other countries as opposed to the United States, this consideration is already possible within the framework of existing laws and regulations. Biltricide, the brand name for the Miles version of praziquantel, was recently approved after just 1 year by the FDA and thus can be now exported wherever it is needed, wherever there are funds to pay for it, and I say that because that is really what the issue is with praziquantel. It got approved here very quickly, even though we do not have any schistosomiasis in this country because it was easily recognized by FDA and USAID that there is a need for the drug, even though it has more dangers than you might accept for an antihistamine, it is for treating a serious disease, let us get it approved quickly. We have that capacity now. Why pass new laws for this particular problem when I would bet that any example that could be cited in the last few years where we have an expedited drug approval system for important drugs such as this, we can get it through without any new legislation.

The final point I would like to make has to do with the study just published by the Department of Commerce in December of 1984 on the whole question—it is called "The Competitive Assessment of the U.S. Pharmaceutical Industry," and it found that our industry "overall remains highly competitive vis-a-vis foreign competitors," and that American companies have "performed well with respect to nearly every measure of competitiveness for which data was available."

It goes on to describe very favorable aspects for increased foreign demand for drugs, U.S. drugs at a 10 to 11 percent annual rate with worldwide sales doubling by 2000. While U.S. companies have been complaining about restrictions on the export of unapproved drugs, the report points out that the United States became the world's leading drug exporter in 1982, beating out the former leader, West Germany. In that year, we had over 20 percent of the total export of drugs by OECD, the 22 OECD countries, and that in the 7 years between 1975 and 1982, we had gained much more than any other of the 22 OECD countries.

Acknowledging the down side, the so-called down side of tighter drug regulation in this country, the report pointed out that "these standards—and the international reputation they enjoy because of the American drug regulation system—provide a competitive advantage to U.S. brand producers in foreign markets." And I would add that this is an important accompaniment of our properly tight but flexible, such as in schistosomiasis, system that we have here. We are looked to as the standard of excellence and I would hate to see that diluted by allowing the export of unapproved drugs out of this country to Western Europe and the rest of the world as would inevitably happen.

The paradox of the double standard, just in closing, is an interesting one. On the one hand, it is said that these countries have comparable drug regulatory systems; on the other hand, it is said that there is a drug lag. You cannot have it both ways. There is a drug lag. Fortunately, most of the drugs are duplicative as in 20 versions of Valium or other drugs, duplicative of drugs that are already available here. But our tighter standard is an important one and it is why so many dangerous drugs get approved in the United

Kingdom, Italy, Great Britain, and other "acceptable countries," and will continue to that do not get approved here. We do not want to be manufacturing those drugs and killing foreigners.

[The prepared statement of Dr. Wolfe and additional material supplied by him follows:]

PREPARED STATEMENT OF SIDNEY M. WOLFE, M.D.

Mr. Chairman and Members of the Committee.

Public Citizen appreciates your invitation to testify today on the subject of the export of unapproved drugs. Public Citizen, the nationwide consumer research and advocacy group founded by Ralph Nader in 1971, is supported by 80,000 grassroots members. Public Citizen is represented here today by Sidney Wolfe, M.D., director of Public Citizen's Health Research Group and Nancy Drabble, Director of Public Citizen's Congress Watch.

A. INTRODUCTION

Public Citizen vigorously opposes any legislation that would allow American drug companies to manufacture and export to international consumers any drugs which have not been found by our Food and Drug Administration (FDA) to be acceptable for sale to American consumers. We opposed S.2878, introduced in the 98th Congress, and we find that the draft legislation dated December 26, 1984 circulated by Genentech, Inc. shares the flaws of S.2878.

We have attached to our testimony and submit for the record a list of 19 health, consumer, international, religious, and labor organizations which were not invited to these hearings that oppose allowing exports of unapproved drugs. We also submit for the record a sample of the many letters we have received from foreign doctors, health professionals and organizations opposing the export of unapproved drugs into their countries.

We have just received a telegram from Health Action

International, a consumer health advocacy organization associated with the International Organization of Consumers' Unions:

"Participants at Health Action International 2 June meeting at Iserlohn, West Germany, strongly condemn efforts to allow the export of FDA unapproved drugs from the U.S. The 62 participants from 17 countries in Europe, North and Latin America, Africa and Asia are shocked that the U.S. should be contemplating such a retrogressive step.

We strongly oppose any U.S. move to derestrict drug exports because:

1. It would run directly counter to the growing tide of professional, medical and consumer opinion which sees an urgent need to rationalize drug use.

2. It should greatly increase the likelihood of inessential, irrational and harmful drugs being marketed in developing countries.

3. It would stand in stark contrast to vigorous FDA controls on the home market which have long been a model for other countries.

We urge members of the U.S. Congress and Senate to join in opposing any bill which would deny citizens of other countries the protection that U.S. Citizens have come to expect. Virginia Beardshaw."

We have also had a communication last week from world-reknowned British pharmacologist and physician at Charing Cross Hospital in London, Dr. Andrew Herxheimer, editor of the Drug and Therapeutics Bulletin, sent by the government to all physicians in the U.K.:

"I am the editor of a long established independent drug bulletin for prescribers, published in England and distributed in translation through Latin America, and the chairman of a new association of editors of drug bulletins around the world. The proposals to permit the export of unapproved drugs from the U.S. fills me with dismay. The drug regulatory system in most developing countries is too weak to keep out ineffective or hazardous drugs, as is recognized by a compromise proposal to restrict exports of unapproved drugs to countries with well-constituted drug authority such as the Federal Republic of Germany. However, any drug could be promply re-exported to any other country, thus defeating the objective of the restrictions. Doctors in third world countries are starved of independent information about medicines and get most of their information from the pharmaceutical companies. They will not be able to resist the powerful sales effort. Perhaps even worse is the fact that most drugs, which in the U.S. and other developed countries are dispensed only on prescription can be freely bought over-the-counter in developing countries. Acceptance of the provision to permit the export of unapproved drugs would seriously damage the health in developing countries."

On December 4, 1984, in protest to the legislation introduced by Senator Hatch (S.2878), hundreds of Thai pharmacology students picketed the American embassy in Bangkok, Thailand carrying signs saying:

"We protest the inhuman double-standard policy of the U.S. Thailand is not a dumping ground for U.S. garbarge." A Thai government health official was quoted in the South China Morning Post (12/5/84) as saying "it must be remembered that the Thais are not laboratory rats to be used for testing medicines".

The drug industry has made significant contributions to the general health and welfare of the world population. However, experience has repeatedly demonstrated the avoidable perils of many drugs. Public Citizen is committed to assuring that the manufacturers and regulators of drugs responsibly and adequately anticipate, recognize, and confront the dangers associated with drugs. The export of drugs not approved for domestic use poses risks to international consumers including Americans living in these countries. Taking these risks is not merited by the supposed benefits of permitting such exports.

B. PUBLIC CITIZEN GENERALLY OPPOSES THE EXPORT OF UNAPPROVED DRUGS

1. Ethical Considerations

The most fundamental argument against the manufacture and export of unapproved drugs is that it establishes a double standard, which violates our basic belief that the health and safety of international consumers is no less important than that of American consumers.

The drug industry has noted that the United States is the only country to impose the same requirements on drug exports as it does on products available for domestic use. However, the failure of other countries to control their drug exports responsibly is hardly justification for us to intentionally decide to do the same.

The industry argues that drugs not approved for sale in America will continue to be supplied to international consumers by our foreign competitors or by American companies with foreign production facilities. Thus, they say that the proposed change in the FDCA will not cause any lowering of the quality of drugs already available but will instead result in keeping jobs, capital and technology in America. We will consider these claims elsewhere in our testimony, but must observe that such factors do not stand up against the fundamental repugnance of codifying an explicit double standard in American law. Moreover, these factors are irrelevant to our obligation to ensure to the best of our ability that American-based companies are not responsible for exporting risks and hazards to foreign consumers. While the United States has no direct power to control the foreign activities of American companies, we can control what goes on inside our borders. That is why we can insist that American and other drug companies acting inside America remain subject to American laws and standards in _all_ of their endeavors.

2. _The "Tropical Disease Exception"_

There are some who believe that the only exception to current law's prohibition against exporting unapproved drugs would be to allow the American manufacture and export of drugs for rare tropical diseases which occur only in certain foreign countries. However, the industry is not known for extensive research and development of such products since it has little economic incentive to develop a drug for such a limited market. But even if there are "tropical disease" type drugs which must be given special consideration due to the different public health import of these diseases in other countries, such consideration is already possible within the framework of existing laws and regulations. The new schistosomiasis drug Biltricide (praziquantel-Miles) was recently approved by FDA and can thus be exported wherever it is needed (wherever there are funds to pay for it). In addition, the Genetech proposal only allows exports of an unapproved drug when another industrialized nation has approved the drug. Since Western Europe provides no market for Third World diseases, there is no reason to think companies would seek approval for drugs for tropical diseases there.

3. Health and Safety Considerations

The American manufacture and export of drugs not approved for domestic use would threaten the health and safety of foreign consumers. In addition to creating a new source of drugs which do not meet FDA standards, such a change in the law would create a new category of drugs available on the world market -- drugs not approved by the FDA but which would nevertheless carry the "Made in the USA" label. Because consumers throughout the world associate the "Made in the U.S.A." label with the highest standards of quality and safety, companies that market unapproved drugs in foreign countries would be in a position to exploit that association unfairly by advertising and labeling their product as "Made in the U.S.A." or simply as made by an American company. Genetech's proposal, which would regulate labeling only on the product's shipping package, would do nothing to address this problem. The proposal ignores wholly the issue of physician and consumer labeling and advertising, where the abusive effects are most likely to occur. The export of unapproved drugs would even have an impact on the health and safety of Americans. In testimony addressing a previous proposal to allow the export of unapproved drugs, a representative of the Ford Administration noted that "control of domestic marketing of such drugs [whose investigations have been terminated on the basis of safety considerations or which have never been approved here because of lack of substantial evidence of efficacy] would be undermined because they could still be legally produced domestically." Drug Safety Amendments of 1976: Hearings before the Subcomm. on Health and the Environment of the House Comm. on Interstate and Foreign Commerce, 94th Cong., 2d Sess. 274, 279 (1976) (testimony of Theodore Cooper, M.D., Assistant Secretary for Health, HEW). This would only heighten the magnitude of the recent disaster of the sale of unapproved drugs such as E-Ferrol. We have yet to see a proposal that would provide adequate safeguards against the variety of scams that drug companies or unscrupulous third parties could exploit of if unapproved drugs are manufactured here in the U.S.. Congress should also not ignore the health and safety concerns of Americans living or travelling abroad who would be subjected to unapproved drugs which bear the "Made in the USA" label. Such people are perhaps the most likely to seek out American-made products. Ironically, any systematic effort to protect Americans abroad from the risk of using unapproved exported drugs would only dramatize the unfairness of a double standard. For example, would Congress countenance warnings in Peace Corps handbooks against the use of unapproved American-made drugs while it permitted American companies to sell those same drugs to the foreign people among whom the Peace Corps volunteers lived and worked?

4. International Political Considerations

In evaluating drug export legislation, Congress must also consider international political factors. America's reputation as a trading partner, as a leader in foreign relations, and as the standard-setter in health and safety matters is at stake.

The export of drugs not considered acceptable for our own people jeopardizes the status of the label "Made in the USA," which is recognized worldwide as evidence of the highest quality. Many countries look to our drug laws, decisions and enforcement mechanisms as models for their own systems.

Changing the law now would also discourage the international trend toward the tightening of controls over exports of drugs and other hazardous products. Such strengthening actions have been taken or are being considered by the Council of Europe, the European Parliament, the Organization of American States and the United Nations, as well as individual countries and regional groups of countries. American Drug export legislation would be seen as a repudiation of the trend toward more stringent regulation and of the worldwide efforts of international health and consumer groups to curb the abusive marketing practices of multinational drug companies. We must continue to set high standards rather than let the conduct of others dictate weaker standards for us.

C. S.2878 AND THE GENENTECH PROPOSAL CONTAIN FATAL DEFECTS

Public Citizen opposes S.2878 and the Genentech proposal. In addition to raising the general concerns discussed above, such proposals are objectionable because of the following specific deficiencies.

1. Exclusion of Antibiotics

If Congress does anything to amend current law, it should simply prohibit the currently allowed export of unapproved antibiotics. This inconsistency in the current law has allowed American drug companies to export unapproved antibiotics and engage in unethical marketing practices, such as promoting drugs for unapproved or prohibited uses, failing to provide adequate warning of potential side effects and hazards, and overstating benefits of drugs. These practices and their results have been described by Dr. Philip R. Lee in his books and in testimony to this Committee.

Both S.2878 and the Genentech proposal would continue to allow unrestricted export of unapproved antibiotics. They fail to extend even their meager protections to antibiotics, thus creating an additional double standard. Thus, both proposals would perpetuate the inconsistency in the current law and the abuses which this inconsistency make possible.

2. Problems with Foreign Drug Approval Decisions

Both S.2878 and the Genentech proposal would rely on actions of a foreign country with an "adequate" drug approval system to trigger exports of an unapproved drug. The Genentech proposal lists 12 countries and would allow the FDA to add or subtract from the list. Unfortunately, this system utterly fails to give the international consumer protection from the potential dangers of unapproved American drugs.

Thus, the safety and effectiveness determinations that would apply to drugs manufactured in America and exported with the "Made in the USA" label would be made by any one of a number of foreign countries on the HHS list. The proposal's definition does not include the requirement that an adequate drug approval authority rely on a standard of safety and effectiveness comparable to the standard in section 505 of the Food, Drug and Cosmetic Act, nor does it include a requirement that well-controlled clinical studies be submitted to demonstrate safety and effectiveness.

As a result, under S.2878, foreign consumers would be subjected to the worst drugs available in each listed country--the lowest common denominator of protection. Every country can be expected to make a few mistakes in its drug approval decisions. Generally, citizens in each country are subjected only to mistakes of their own country. But under S.2878 Third World countries could receive the bad drugs approved in every country on the list. As we will discuss below, we believe that the Genentech proposal, despite its cosmetic appearance, would have the practical effect of facilitating the sale of unapproved drugs in the Third World as well.

A threshhold consideration is whether Congress should put itself or HHS in the position of having to name countries with "adequate" drug authorities and simultaneously, by omission, identify others as having inadequate authorities. Congress should not assume (nor would the State Department want it to assume) this politically awkward responsibility, and the FDA last year told this Committee that the FDA does not want it either.

The list of "adequate" countries is the only provision for any significant health and safety assessment of drugs to be exported. Apart from the feasibility of the list, additional problems of simple logic stem from the term "adequate health authority to approve drugs," which is used in both proposals. It is commonly recognized that the United States has the most stringent drug approval process in the world. If the FDCA and the FDA are the standard as they necessarily must be, then deciding how much less protection is still good enough would involve an ultimately self defeating course of conceptual gymnastics. S.2878 provides no guidelines for making the decision and the additional language of the Genentech proposal merely restates the contradiction.

There is a considerable list of examples proving that other countries' drug approval authorities provide less protection than ours does -- examples of drugs approved by sophisticated countries but not here, with disasterous results. Dr. Barbara Moulton has previously testified on this in detail. Oversight, the FDA's Process for Approving New Drugs: Hearings before the Subcomm. on Science, Research and Technology of the House Comm. on Science and Technology, 96th Cong., 1st Sess. 398-402 (1979). Among the examples offered by Dr. Moulton were the following:

- Thalidomide - across Europe, thousands of still-births and tragically deformed children, some of them brain damaged.

- * Isoproterenol Inhalers - 3,500 deaths in England and Wales, mostly teenagers, from a highly concentrated form of isoproterenol used in inhalers for asthma.
- * Aminorex - hundreds of cases of primary pulmonary hypertension, including 26 deaths in Switzerland.
- * Stalinon - at least 110 deaths in a small French town as well as other cases elsewhere in France.
- * Practolol - many serious side effects (including permanent or near-permanent blindness, and the growth of a strangulating membrane in the bowels leading to death during corrective surgery). Ironically, this drug was used as an example of a drug denied to the American Public because of the "drug lag."

Dr. Moulton also cited the following toxic drugs which have been permitted abroad, but not in the United States: Guanoxan; Sordinol; Pronethalol; Triflocin; Cinanserin; MK-665 (Ethynerone plus Mestranol); Chlormadinone Acetate; and Hexobendine. See also E.C. Lambert, Modern Medical Mistakes (1978).

Since the U.K. appears on the approved list of 12 countries in the Genentech proposal, it is instructive to look at what has happened quite recently in that country. As shown on the chart below, 6 prescription drugs, all approved in the U.K. but none approved in the U.S., have been taken off the market in just the past two years because of dangers -- including a large number of deaths.

One of the most dangerous and widely marketed of these was Osmosin, a slow-release arthritis drug. It was approved in December, 1982 in the U.K. and later in West Germany. It was also approved in the Netherlands, Sweden, Switzerland, and other countries which might be said to have "adequate" drug regulatory systems. In September, 1983, Osmosin was banned worldwide because of 38 deaths and over 400 adverse reactions, many life-threatening. Unlike other arthritis drugs, Osmosin caused intestinal perforation, fatal in several instances.

These most recent examples can be added to older examples cited in two recently published studies* to get a complete accounting for the past 24 years. Including the 6 drugs shown in the chart, there have been a total of 17 drugs removed from the market in the U.K. for safety reasons since 1960 which were never approved in the U.S. During the same interval, only 3 drugs were taken off the market here which had not been approved in the U.K. Although the authors of these studies conclude that the safety withdrawals are similiar in the two countries, there are two problems with their analysis. First, they blur the distinctions by including drugs approved and banned in both countries (Oraflex, Zomax, etc.). Second, they necessarily omit this most recent alarming streak of 6 U.K. bans.

This comparison of the U.S. and English record shows that the standards for drug approval are more stringent in this country and that allowing exports of unapproved drugs is truly a double standard. Had any of these 6 recently banned U.K. drugs been manufactured in the U.S. -- as this proposed legislation would allow -- U.S. companies would have been responsible for deaths and injuries of foreign consumers, smearing the "Made in the USA" label with the blood of foreigners.

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* Clinical Pharmacology & Therapeutics 35, p. 559-566, 1984, and an FDA study: New Drug Introductions, Discontinuations, & Safety Issues in the U.S. & the U.K., January, 1984.

DANGEROUS DRUGS WITHDRAWN DURING 1983 AND 1984 FROM THE U.K. MARKET BUT NEVER APPROVED IN THE U.S.*

DRUG (BRAND/GENERIC)	USE	DANGER	TAKEN OFF U.K. MARKET
ZELMID zimelidine	Antidepressant	Guillain-Barre; paralysis	9/83
OSMOSIN slow-release indomethicin	Arthritis	38 deaths; intestinal perforation	9/83
FLOSINT indoprofin	Arthritis	Deaths; gastro-intestinal reactions	12/83
METHRAZONE feprazone	Arthritis	Poor overall adverse reaction profile	3/84
ALTHESIN alfadolone	Anesthetic	Anaphylactic shock	5/84
FLENAC fenclofenac	Arthritis	Deaths; bleeding	6/84

*During 1983 and 1984 no drugs were withdrawn in the U.S. which were approved here, but not approved in the U.K.

3. Sales to Third World Under S.2878

S.2878 makes it legal to market a drug in a foreign country which is not on the list -- in other words, a third-world country. Clearly, this is a lesser standard than requiring the affirmative and informed approval of the drug by the importing country's regulators.

Many books and studies have documented both the inadequacies of drug regulators in less-developed countries and the unethical practices of the international drug industry operating in such countries. These include Prescriptions for Death and Pills, Profits and Politics, both by Milton Silverman, Mia Lydecker, and Philip Lee; Bitter Pills: Medicines and the Third World Poor by Diana Melrose (OXFAM); Pills, Pesticides and Profits: The International Trade in Toxic Substances by Ruth Norris; "Pesticides and Pills: For Export Only" (film) by Robert Richter; Insult or Injury? by Charles Medawar (Social Audit); and Hungry for Profits: U.S. Food and Drug Multinationals in Latin America by Robert Ledogar, as well as Congressional testimony and United Nations studies. Many developing countries lack the funds, expertise and government structures to protect their citizens from drug-related dangers. In some, the approval and enforcement systems are often short-circuited by bribes and other illegal conduct by some drug companies. The Securities Exchange Commission, when it was more vigorously enforcing the Foreign

Corrupt Practices Act, documented many examples of such practices by American drug companies.

These problems are compounded by widespread unethical marketing practices of the drug industry: drugs are promoted for uses which are prohibited in the U.S. and other developed countries; warnings of side effects and hazards are inadequate or totally omitted; expensive drugs are pushed when cheaper alternatives, or no drugs at all, would be as or more effective.

Obviously, we have very little ability to control actions which take place outside of our own borders. But in deciding what actions are to be permitted inside our country, we cannot ignore the effect of our decisions in the third world. It would be unrealistic for us to assume that decisions of foreign authorities -- or their failure to make decisions -- will provide their citizens with sufficient protection from unapproved drugs shipped from the U.S. when we know that even under the status quo those authorities are failing to provide protection.

Even if we assume that some or all of the countries not on the HHS list have the ability to make reliable decisions about which drugs they will import, S.2878 does not give them sufficient information to make informed decisions. There is no requirement that the officials of these countries receive the kind of information which must be given to the FDA to support an application for U.S. approval. In fact, there is no provision requiring that the importing country be provided with any information before it certifies that sale of the drug would not violate its laws. And even after the export of the drug begins, the proposal limits the information which is to be provided foreign authorities to that which is available to the American public.

4. Failure to Prevent Reshipping of Drugs to Third World Under the Genentech Proposal

The Genentech proposal allows shipment of unapproved drugs to industrialized nations. Unfortunately, it contains no safeguards to prevent reshipment of unapproved drugs to third world countries. Western Europe could become a mere way station for drugs on their way to underdeveloped countries particularly since Western European countries do not themselves restrict exports; the drug industry's miserable record in Third World nations provides little reassurance that the industry would not take advantage of this gaping loophole. The Genentech proposal fails to ban reshipment explicitly and imposes no sanctions on violating companies. The effective result would likely be an uncontrolled flow of unapproved drugs to the Third World; thus, the limitation on exports to Western Europe and Japan remains only a cosmetic change rather than a legitimate compromise.

5. Export Approval by FDA Inaction

Both S.2878 and the Genentech proposal would prohibit the export of drugs subject to final agency action denying, withdrawing, or suspending their approval or otherwise banning them. Unfortunately, this provision would permit the export of drugs voluntarily withdrawn from the market or from the application process, even if such withdrawal were precipitated by safety problems with the drug. Since the FDA often allows companies to withdraw applications that the agency would otherwise deny, this provision would add only a minimal additional protection measure to the bill while leaving a huge loophole in the purported protections in the proposal.

S.2878 contains important procedural defects. Except where the proposed export is supposedly justified by particular diseases or health conditions in the importing country which do not exist in the U.S., S.2878 calls on HHS to approve *de facto* the proposal to export: if specified findings as to the export's health and safety impact on both the importing country and the U.S. are not made within a limited period of time, the export is allowed.

Similarly, the Genentech proposal automatically authorizes the export of an unapproved drug unless the FDA, within ninety days of notification of a company's intention to export, determines that such export would be unlawful. What is more, the FDA's role in making any such determination would be merely ministerial, since the FDA would be authorized only to ensure that eight essentially technical requirements were met. To trigger the export of an unapproved substance by means of FDA inaction, particularly when the FDA is granted no discretionary authority, is highly inappropriate.

While the Genentech proposal affords drug companies notice and an informal hearing to challenge an adverse determination, the proposal does not provide for any public notice, comment or hearing when a company seeks to export an unapproved drug. The absence of public participation and public scrutiny, including public notice and comment, and the opportunity to seek judicial review is completely unjustified in these circumstances,. The export of unapproved drugs necessarily entails circumvention of the normal FDA process of testing and examining drugs. By depriving the FDA of any substantive discretion and cutting it off from the contributions of outside expert commenters, the proposal makes a sham of its supposed protections for foreign consumers.

Action by inaction is inconsistent with a recent FDA statement of policy on the export of drugs for investigational use:

> Requiring affirmative agency response ensures that an inappropriate export request will not be authorized through an inadvertent failure to act. This is especially important in the export authorization context where, once a drug shipment is made, FDA loses control over the the regulated article.

49 Fed. Reg. 2095 (January 18, 1984). An affirmative response, supported by affirmative findings, is even more important when the substance to be exported will be widely available to international consumers without the strict limitations and close supervision which accompany investigational use.

6. Insufficient Discretion and Information for FDA Decision

Both proposals fail to require companies that want to export drugs to provide HHS with information about the drug to be exported. HHS can hardly be expected to act responsibly in exercising any limited veto power if it lacks sufficient information about the drug and the circumstances under which it is to be marketed and used.

Both proposals also fail to provide for any oversight of the industry's export practices or for the revocation of export authority based on related misconduct. In addition, the Genentech proposal does not revoke export authority even if one of the listed countries bans the drug. S.2878 does. Neither proposal precludes export where a drug has been voluntarily withdrawn in a listed country because of safety defects. Thus, approval in a listed country triggers export approval but disapproval in a listed country does not trigger export disapproval.

Finally, both proposals would prohibit export if HHS found that U.S. manufacture would be contrary to U.S. public health and safety. The explanatory statement indicates that worker health is the reason for this requirement. But HHS is not the best qualified agency to consider worker safety. The Occupational Safety and Health Administration should make an affirmative determination that worker safety would not be jeopardized by U.S. manufacture of an unapproved drug. This is especially important in light of the lack of experience and the resulting uncertainties about the safety of new biotechnological products and processes, such as recombinant DNA.

7. Exports Without Adequate U.S. Testing

S.2878 required completion of Phase I testing before a drug could be shipped to an unlisted country and imposed no testing requirement on drugs shipped to listed countries. The Genentech proposal only requires the pendency of an investigational new drug exemption (IND).

Drug companies argue that they intend to seek approval of their products in the United States, but need to expedite marketing of their drugs in a foreign country. Nowhere, however, does the Genentech proposal bind any drug manufacturer to seek approval for sale in the United States of new drugs it wishes to export. For example, the proposal does not require that the exporting company ever submit or complete a New Drug Application for the unapproved drug. Thus, contrary to its stated purpose, the legislation would authorize a company to export an unapproved drug even if the company failed to submit an NDA, let the NDA lapse, or even if a submitted NDA failed to win FDA approval.

Merely requiring a current application for an IND does not ensure that a company will seek FDA approval or that sufficient tests have been conducted to reveal the drug's risks. According to the 1982 Report of the Commission on the Federal Drug Approval Process, only about 10% of the drugs tested under IND's in Phases

I and II even proceed to Phase III clinical trials, let alone to the submission of an NDA. In addition, the early Phase I trials involve the administration of the investigated drug to only a small nuber of patients: from a few to no more than 300. Only Phase III trials encompass large patient samplings in the range of 2000 or more.

1. The Charge of Paternalism

Some proponents of the export proposal claim that opposition to the export of unapproved drugs is paternalistic, and that we should let other countries decide what is best for their own citizens. As has already been observed, even if we assume that all countries are in a position to make such decisions, the current proposal denies other countries adequate information to make their own informed decisions.

The industry is considerably less inclined to advocate the right of other countries to self-determination when this works against the industry's interests. When Bangladesh promulgated an essential drug list in 1982, removing from the market 1742 dangerous, ineffective, useless or unnecessarily expensive drugs, the industry pushed the State Department to put pressure on the Bangladesh government to rescind its decision. And now, the industry is doing everything in its power to force the rescission of a new Mexican policy limiting drug exports to Mexico and activity inside Mexico by non-Mexican firms.

The paternalism argument is superficially most persuasive for Western European countries. But current law does not restrict the actions of industrialized countries; it merely expresses the policy that the U.S. should not participate in the foreign sales of products which it will not allow to be sold in our own country. Companies that produce drugs in the U.S. should be subject to American standards. Also, as discussed above, once a drug can be manufactured here and exported to any one country, it would be difficult to prevent re-exports to any other destination.

2. The Industry's Jobs Forecast

The industry claims that the existing ban on the export of unapproved drugs has forced American drug companies to locate some of their production facilities abroad, resulting in a loss of jobs, investment and technology here. Some members of the industry have prepared estimates of the volume of activity that is likely to be generated by the enactment of the industry's proposal. These estimates were scrutinized and discredited by the Labor Institute in its statement last year to this Committee. In particular, industry job estimates are grossly inaccurate and inflated. In its testimony last year, American Cyanamid claimed that lifting the unapproved drug export ban would create up to 50,000 new U.S. jobs. But, as the Labor Institute explained, the most likely new employment would be production work since research, management, and marketing primarily remain in the U.S. even when production is carried on overseas. The Pharmaceutical

Manufacturers Association 1980-1983 Annual Survey reports that the domestic drug industry employs only 69,000 production workers, showing that the drug industry is not labor intensive. Thus, American Cyanamid's alleged 50,000 new jobs would mean a 70% increase. Even if one generously included jobs in allied industries, the figure is patently ridiculous.

Requests for examples of specific products which except for current law would have been manufactured in the U.S. have received minimal response. One company has stated that it would "clearly prefer" to manufacture in the U.S. certain substances now being developed, without indicating why this is "clear."

In arguing for drug export legislation industry repeatedly fails to acknowledge the multiple factors which work against any decision to manufacture unapproved -- or even approved drugs -- here. These include labor costs, international exchange rates, other countries' domestic production requirements, tariffs, pricing factors, proximity to the the international market, the uncertainty of American approval, and the uncertainty of the drug's acceptance on the marketplace.

Nevertheless, some companies might locate some new production facilities in the U.S. if the export proposal were enacted. It should be noted that a significant proportion of any such facilities -- and the jobs which go with them -- would likely be located in Puerto Rico, where there is virtually no union presence. An increasing amount of current drug industry activity is located there, to allow manufacturers to take advantage of lower income taxes under Section 936 of the Internal Revenue Code, lower interest rates on industrial revenue bonds, and lower labor costs.

3. Competition with European Companies

The industry argues that restrictions on drug exports should be lifted to help American companies compete with European firms. But a recent Commerce Department report, "A Competitive Assessment of the U.S. Pharmaceutical Industry," found that U.S. industry "overall remains highly competitive vis-a-vis foreign competitors," and that American companies have "performed well with respect to nearly every measure of competitiveness for which data was available." It goes on to describe very favorable prospects for increased foreign demand for drugs at a 10%-11% annual rate, with worldwide drug sales doubling again by the year 2000. While U.S. companies have been complaining about restrictions on the export of unapproved drugs the report points out that the U.S. became the world's leading drug exporter in 1982, beating out the former leader West Germany.

It is of interest that the report shows the U.S. to have made the biggest gain (from 14.52% [1975] to 20.07% [1982]) of the total OECD countries' exports of any of the 22 OECD countries in the interval between 1975 and 1982, surpassing even West Germany by 1982.

Acknowledging the so-called down side of tighter drug regulations here, the Report nevertheless points out that "these standards (and the international reputation they enjoy) provide a competitive advantage to U.S.-brand producers in foreign markets."

This report hardly paints a picture of an industry that needs a new loophole in the law to provide economic relief. Industry may also raise a U.S. balance of trade argument, but balance of trade problems stem from the strong U.S. dollar, not drug export limits.

4. Transfer of Biotechnology

The drug industry and particularly some biotechnology firms argue that requiring foreign manufacture of unapproved drugs results in the transfer of technology from the U.S. to foreign countries.

No estimates of the volume of technology transfer has been provided by the industry. A recent report by the Office of Technology Assessment reported that:

> Most observers would agree that the net flow of biotechnolgy is outward from the United States, but such judgements are impressionistic at this time. Also, the net flow of technology outward from the United States is likely to diminish as foreign companies enter the U.S. market (via subsidiaries or foreign manufacturing operations) bringing with them foreign technology.

Office of Technology Assessment, Commercial Biotechnology: An International Analysis 454 (1984).

Nor has the industry discussed the main reasons why biotech companies transfer technology or enter into foreign joint ventures. As discussed in two recent and exhaustive articles in the Washington Post, limits on drug exports have little to do with the biotech industry's motivations for sharing technology with foreign firms. The real reasons are;

(1) biotech firms need foreign capital to finance research because the flow of American venture capital has slowed;

(2) foreign countries have engineering personnel and biotech production facilities not available in the United States and smaller biotech companies cannot finance the capital-intensive development and construction of their own U.S. plants. A recent National Academy of Sciences report documented how U.S. companies lag in biotechnology processing, particularly compared to West Germany, Japan, and Britain. Thus, even if biotechnology firms could manufacture their unapproved drugs here, it is unlikely they would do so since they can move into the market more quickly using foreign plants. In fact, only a large biotech firm like Genentech would likely take advantage of a change in the law, leaving smaller companies at a competitive disadvantage.

(3) Foreign partnerships allow U.S. companies into overseas markets that would be otherwise inaccessible because of the foreign country's desire to develop its own biotechnology industry. "You need a Japanese partner to be successful in Japan--it's just the nature of the marketpalce," said Barry Weiner, executive vice-president of ENZO Biochem Inc. in the Washington Post article. Even large companies such as DuPont have formed joint ventures, citing the usefulness of the marketing ability of foreign companies in their own regions.

(4) Biotech companies gain scientific and production knowledge through foreign partnerships. Thus, new technology is also transfered to American companies. For example, U.S. companies can benefit from Japanese expertise in fermentation processes and may be able to apply that knowledge to development of other products. Harvey Price, executive director of the Industrial Biotechnology Association said to the Post, "But for most companies, at the present stage of development, relationships between corporations that cut across national lines are beneficial to both parties. The Technology transfer goes both ways."

(5) The largest technology transfer occurs in scientific journals, research institutes, universities, and conferences. Drug companies must submit detailed test results to foreign countries to gain approval. Export of unapproved drugs would not alter this requirement in any way.

In sum, the speculative nature of the industry's argument is enhanced by the uncertainty over whether particular biotechnological products will in fact be approved abroad first, or at all. The aforementioned Commerce Department report states that "nationally, in terms of recombinant DNA guidelines, those of the United States are the least restrictive."
The case made by the industry neither confronts nor overrides the ethical and the health and safety concerns raised by the prospect of legislating a double standard of protection.

E. DRUG EXPORTS -- AN OVERVIEW

The drug industry argues that because the United States' drug approval process is slower than its counterparts in other countries, many good drugs which will ultimately be approved by FDA are approved abroad first; as a result, current law forces American drug companies to manufacture unapproved products abroad in order to remain competitive on the world market. Once a drug is approved here, says the industry, it is unlikely that production will be transferred back to the U.S. The drug companies testify that they would prefer to manufacture here in the first place.

Their proposed solution is to create a double standard of protection. They would allow American companies to domestically manufacture and to export to international consumers drugs which cannot be sold to American consumers because the drugs have not been found by the FDA to be safe and effective.

To the extent that U.S. drug approval takes longer because our laws impose higher standards, delays in approval must be accepted. To the extent that any delays are caused by problems in the laws and their enforcement, these problems should be addressed directly, so that American consumers can benefit as well. But the enactment of a double standard of protection -- one rule applicable to us, and one applicable to everyone else -- is clearly not the proper response. The lives and health of international consumers must not be jeopardized to subsidize the economic interests of any individual or any industry.

OPPONENTS OF THE EXPORT OF UNAPPROVED DRUGS

American Public Health Association
Associated Pharmacologists and Toxicologists
Australian Consumers Association
Consumer Federation of America
Consumers Union
Freres des Hommes (Belgium)
Friends Committee on National Legislation
Health Action International
Information Center Against Drug-Induced Suffering (Japan)
Interfaith Center on Corporate Responsibility
International Chemical Workers Union
International Organization of Consumers Unions
Labor Institute
National Women's Health Network
Natural Resources Defense Council
Public Citizen (Congress Watch, Health Research Group)
United Church Board for World Ministries (United Church of Christ)
United Methodists
Village Independent Democrats (New York City)
Voluntary Health Organization of India

SEPTEMBER 12, 1984

The New York Times

Founded in 1851

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Don't Export Unapproved Drugs

Selling foreigners drugs not yet approved as safe for Americans would create an invidious double standard unhelpful to all American drugs sold abroad. Yet the Senate Labor and Human Resources Committee is considering a bill that would permit just that.

Present law forbids the export of a drug until it's been approved by the Federal Food and Drug Administration. Because the tests are so stringent, drugs are often approved first abroad, and American companies will start production there.

The pharmaceutical industry wants the right to export drugs still under test by the F.D.A., provided they are approved by at least one other country with a competent review authority. This would help keep both jobs and technology at home, the industry asserts, because production could then start and continue in America instead of in the approving country.

That's a rosy argument, full of hidden thorns. Most drugs that enter the F.D.A.'s testing process never complete it. They fail because as more and more patients are exposed, insidious side-effects that escaped detection in preliminary trials often become apparent. No one suggests that drugs deemed unsafe for Americans should be sold abroad, yet many of the drugs exportable under the Senate's bill would certainly prove to be unsafe once testing is completed.

Further export would then be halted, but in the meantime the unsafe drug may have caused widespread harm. Flenac is an arthritis medicine that received approval in Britain and would have been exportable under the Senate's bill. It's now been ordered off the British market after causing 15,000 adverse reactions and an unstated number of deaths.

The Senate bill would make an untested drug exportable if approved in any of eight foreign countries, surrendering the decision power to the country with the laxest review. If the F.D.A.'s standards are too high, let them be revised, not circumvented.

American Cyanamid, a leading exporter of drugs, has told Congress the bill would create 50,000 new jobs in the United States. But the International Chemical Workers Union, the industry's largest, strongly opposes the bill and calls its potential effect on jobs "greatly exaggerated." Export rules aside, pharmaceutical companies would often produce drugs abroad for other reasons, such as cheaper labor or environmental controls.

The Food and Drug Administration's tighter rules may be a regrettable handicap in vying with foreign competitors. But extra safety is not a bad selling point. And should an American-made thalidomide ever slip into international commerce, as is possible under even the most thorough review, a double standard will look a lot worse than a single one.

The Boston Globe

Founded 1872

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9/14/84

Exporting unapproved drugs

Congress must not allow American pharmaceutical companies to set an immoral double standard by exporting drugs that have not been approved for use in the United States. A bill under consideration by the Senate Labor and Human Relations Committee would permit such exporting. It must be defeated.

The export of untested drugs is wrong. Permitting their sale would impose unnecessary risks for people, especially those in underdeveloped nations that do not have adequate drug-testing programs.

Existing law requires approval by the Food and Drug Administration before a drug is exported. The FDA drug-testing program is rightfully stringent, and it can take years before market approval is given for a product. The bill before the Senate committee would allow the export of a drug if it is approved by another country with a competent testing program.

The American pharmaceutial industry argues that it is losing sales to foreign competitors because of tough FDA standards. The industry, which often starts production of unapproved drugs abroad, also contends that the Senate bill will help to keep jobs and technology at home. The Reagan Administration has sided with the drug companies.

Consumer groups point out the hazards of the legislation. In testimony before congressional committees they have named drugs, believed to be harmful, that could have been made in America for export if this bill had been in effect. These include Zelmid, an antidepressant with an adverse effect linked to a form of paralysis that is often temporary but sometimes fatal; Osmosin, an arthritis medication suspected in 38 deaths; and Flenac, another arthritis medication that was recalled in Britain after causing 15,000 adverse reactions and an unknown number of deaths.

Sen. Edward Kennedy has offered several amendments aimed at adding some safeguards to the drug-export bill. One would require American consuls and embassy personnel to keep track of the drugs and see that safety requirements are met. The amendments are vital if the bill is to be passed. But it will be far safer for foreign consumers if common sense and decency prevail.

The responsibility for monitoring American-made drugs should not be shifted to a foreign country. It would be almost impossible for the FDA to monitor these drugs abroad. The FDA has a hard enough time ensuring proper reporting of drug reactions in this country, as is evident from the large number of drugs belatedly recalled in recent years. If the drug industry believes that FDA standards are too strict and time-consuming, it should work to change those regulations.

The Labor and Human Relations Committee is scheduled to vote on the drug-export bill next Wednesday. Congress must not give the impression that the health and safety of foreign consumers is of less importance than that of Americans.

4 Part II/Tuesday, September 11, 1984

Los Angeles Times

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Exporting Trouble

New drugs must pass the toughest approval process in the world before doctors can prescribe them in this country. The tests can take years and delay the availability of some new medicines but they provide a margin of safety for patients.

The Reagan Administration says the delays are bad for the pharmaceutical business and ultimately drive American jobs to foreign countries. It is backing a bill that would allow businesses to export medicine that has not yet been approved for American consumption.

That is a bad idea, a position that says that it is all right for foreigners to face health risks that Americans do not face, a position that would turn the rest of the world into guinea pigs.

A bill that would repeal the current ban on such exports, sponsored by Sen. Orrin G. Hatch (R-Utah), is tentatively scheduled for a vote Wednesday by the Senate Labor and Human Relations Committee. Although the bill does have some safeguards, it should be rejected.

Under Hatch's proposal, which the Administration supports, medicine that has passed the first level of toxicity testing by the Food and Drug Administration could be exported. But it is often in subsequent tests that unexpected side effects or other problems are discovered.

Hatch's bill would also require that a country with respectable drug-testing standards, such as West Germany or England, approve the new American drug before it is exported. If a country with relatively high standards disapproved a drug, the Food and Drug Administration would cancel its license. One or more of those countries would have to approve a drug for its own use before the drug could be exported to countries with weak standards or none at all. That is not a good substitute for making the drug pass the the most stringent standards—those of the United States.

The Administration backers, including representatives of the Food and Drug Administration, also argue economics. Some U.S. pharmaceutical companies have located plants abroad because drugs manufactured abroad are not subjected to such intense scrutiny and can often reach international markets years ahead of American products. That costs American businesses dollars and American workers jobs, according to the Administration. But if the new drug export is allowed, will those jobs be relocated in the United States despite the lower wages and other advantages in foreign countries?

The economic argument cannot be used to justify health risks at home or abroad. Lawmakers should not allow the export of medicine until it has been proven good enough for Americans.

The Philadelphia Inquirer

An Independent Newspaper

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SAM S. McKEEL, President

EUGENE L. ROBERTS JR. Executive Editor

EDWIN GUTHMAN Editor

Monday, August 6, 1984

Page 6-A

The cost of exporting trouble

It has been labeled as a jobs bill but in fact it's a greed bill. It's legislation that could cause injury, illness or death. It's a bill that places private profits ahead of public responsibility. It would confirm in many minds that the United States cares less for their well-being than for a fast buck.

The legislation would allow U.S. drug companies to produce new drugs for sale in foreign nations even if those drugs have not been approved for use at home. Current law requires that drugs manufactured in the United States for export meet domestic safety and efficacy standards.

The U.S. Food and Drug Administration and the World Health Organization have endorsed the legislation. "We believe the governments of other nations are in the best position to assess their own health needs," Dr. Mark Novitch, acting FDA commissioner, recently told a House subcommittee considering the bill, which is being sponsored in the Senate by Orin Hatch (R., Utah).

Sen. Hatch and others, led mainly by American drug makers, argue that the existing law forces U.S. companies to open foreign production facilities to get around the safety restriction. (Current law allows U.S. drug firms operating outside the United States to manufacture and sell products abroad that do not meet domestic safety and labeling requirements.)

Supporters claim that if the Hatch bill is enacted, it could create as many as 50,000 jobs and increase drug-export sales by $1.76 billion in five years. Other studies indicate those estimates are vastly inflated. Regardless of the actual numbers, what's the price of changing the law?

Critics claim that the bill would allow American drug makers to flood the markets with products that are untested and would be used inappropriately. These products would be dispensed by untrained personnel whose only source of information would come from drug company salespeople. Few Third World nations have any type of effective drug regulation and most rely on U.S. data.

Supporters of the change argue that they have included some safety provisions to protect against abuses, but those provisions are vague and ridden with loopholes.

For example, the FDA will be required to prepare lists of foreign countries deemed to have "adequate" drug regulation systems. If one of those countries approves a U.S.-made drug for a particular use then that approval carries the same weight as an FDA endorsement and gives the manufacturer carte blanche to distribute it anywhere in the world, regardless of the quality of the testing standards in the approving nation.

Jean M. Halloran, director of Consumer Union's Institute for Consumer Policy Research, which opposes the bill, notes that it would allow U.S. drug companies "to use people in other countries as guinea pigs."

"If a drug is not good enough for us, we shouldn't inflict it on our brothers and sisters abroad," she told the House subcommittee. That may not be the motto of a successful drug company executive, but it's the credo of a good world citizen.

.! 1984

คปอส.

คณะกรรมการประสานงานองค์กรเอกชนเพื่อการสาธารณสุขมูลฐาน

๑๓๒/๑๔ ซอยอรพิน ถนนพระราม ๖ กทม. ๑๐๔๐๐ โทร.๒๗๘๑๘๐๘

The Co-ordinating Committee
For Primary Health Care M.
Of Thai NGOs.
132/14 Soi Oropin, Rama 6 Rd.,
Bangkok, 10400 Thailand

October 15, 1984

JS House of Representatives

The Capitol

Washington, DC 20515

JSA

Dear Sirs,

Regarding the December 5, 1983 draft legislation which would amend the Food Drug and Cosmetic Act to allow the export of unapproved drugs manufactured by US drug companies to the third world markets, we, the Co-ordinating Committee for Primary Health Care of Thai NGOs (CCPN),on behalf of 16 health Development Organizations and Thai drug consumers, strongly object to such proposal owing to various reasons, namely:.

1. The mentioned proposal violates the basic human rights of Thai people or the Third World people, and also goes against the "Universal Declaration Human Rights" because the health and safety of international consumers i no less important than that of American consumers.

2. The mentioned proposal is contrary to the appeal of WHO to all countries over the world to develop a quality of life by means of Primary Health Care and to achieve the goal of Health For All By The Year 2000.Especial the drugs, WHO has prepared the "Essential Drug List" which consists of about 200 kinds of drugs that are approved by experts to be sufficient for curing and healing of most of the diseases of these countries. Now the developing countries are inundated with unapproved drugs, such as Thailand, there are more than 22,000formula which about 46% of them are unapproved or unsafe drugs.Therefore, the legislation which allow export of unapproved drugs in USA will distinctly contravene the purpose of WH

3. The proposal will cause more problem to Thailand's drug consumption; now Thai people are imposed to use the "double standard of drugs", drugs tha labelled "For Export Only", drugs that are on-trial and drugs that have already been banned, because the exporters and manufacturers employ various tactics and even give insufficient or untrue information to make our drug approval authorities accept the products unwittingly.

Such proposal of the US drug industries will therefore seriously worsen the situation of drug utilization of Thai people; thus it will destroy the health of our people.

We, CCPN/Thai NGOs, strongly opposed the proposed legislation and appeal to you, Mr.Chairman and the members , to object also any drug industry proposed legislation that seeks to allow the export of unapproved drugs in consideration of basic equal right of consumers regardless their nations and languages, in addition to the virtue and ethics of a drug exporting country; and the last but not least is that the USA has been a stronger leader in opposing the violation of human right in every country, therefore she should not do so by herself!

The USA has been our good friend for a long time. We do hope that the rejection of such unethical proposal will prove again her cordiality to Thai nation and people.

Yours sincerely,

(Asst.Prof.Sumlee Jaidee)
Chairperson, Health & Development Foundation

Prawase-Wasi
(Prof.Dr.Prawase Wasi)
Chairman, The Co-ordinating Committee for Primary Health Care of Thai NGOs

Netnapa Khumthong
(Mrs.Netnapa Khumthong)
Chairperson, Social sience of Public Health Group

(Pharmacist Suksangap Buasuang
Chairperson, Community Pharmacy Group

R Mantasatien
(Miss Roweewan Mantasatien)
Executive Secretary, Thai Consumers' Power Group

(Miss Ladda Thitikiattipong)
Chairperson, Voluntary Group for Consumers

Umpon Jindawatthana
(Dr.Umpon Jindavatthana)
Chairperson, Rural Doctor Society)

(Dr.Prapoj Petrakard)
Chairperson, Community Health Group

Somfai Sirikanokvilai
(Dr.Somfai Sirikanokvilai)
Chairperson, Chumpaung Primary Health Care Group

(Dr.Sumreung Yaengkratok)
Chairperson, Sungnoen Primary Health Care Group

(Pharmacist Somboon Jateleeja)
Chairperson, Mahidol Pharmacist Alumni

(DentistPaitoon Suriyavongpaisarn)
Chairperson, Rural Dental Health Club

(Mr.Thanin Puranun)
Chairperson, Youth For Consumers

(Dr.Chokchuang Chutinatan)
Chairperson, Consumers Group of Siam

Tawatchai Lim

(Mr.Tawatchai Lim)
Chairperson, Traditional Medicine
in Self-Curing Project

Surakiat Achananuparp

(Asst.Prof.Dr.Surakiat Achananuparp)
Director, Folk Doctor Foundation

AROGYA DAKSHATA MANDAL
[illegible]
Pune 30.
411 030
(India)

आरोग्य दक्षता मंडळ
१११३, सदाशिव पेठ, पुणे - ४११ ०३०.
सार्वजनिक विश्वस्त संस्था.

फोन : द्वारा ४४९११७.

30 August 1984
जा. क्र.
विषय :-

Senator Edward Kennedy
Russel Offices, Room 109
Washington DC 20510
USA

Sub: U.S.Bill on Export of Hazardous Drugs.

Sir,

Bill No. 52878, regarding proposed legislation " to permit US drug producers to manufacture and export drugs that are not approved for use in US " will be shortly introduced in the US Senate.

We strongly feel that this bill is unethical and will directly affect the millions of innocent people of the underdeveloped and developing countries.

We are trying to ban drgus viz oxyphenbutazone, analgin, anabolic steroids, estrogen+progesterone combinations, tetracycline drops & syrup (pediatric use) etc, and your proposed bill is further helping the pharmaceutical sharks to expboit the suffering humanity.

If you decide to legally allow the pharmaceutical firms to manufacture and export dangerous drugs, it will result in disaster. If you, under the pressure of American Drug Industry allow the bill ~~ha~~ to be passed, it will cost US the good-will of the third world people.

We therefore earnestly request you to oppose this bill and see that it is not passed. We thank you,

Yours sincerely,

Dr. W.V.Rane.
Jt. Hon. Secretary,
Arogya Dakshata Mandal.

cc to Dr. S.Wolfe,
Health Research Group,
2000 P St.
N W Suite 708
Washington DC 20036

Dear Mira.
Keep up the good work

Miraj Medical Centre
Miraj, Dist. Sangli
Maharashtra, India 416 410
31 August 1984

Ms. Gwen Crawley
Associate for Health Ministries
Presbyterian Program Agency
475 Riverside Drive - Room 1253
New York, N. Y. 10115
U. S. A.

Dear Gwen:

The following is a copy of a letter to Senator Ted Kennedy written in response to a letter from Dr. Mira Shiva of VHAI, a copy of which is enclosed. I hope you people there will put the pressure on your Senators to defeat this bill. You can see why.

> Dear Senator Kennedy:
>
> Sometimes we are embarrassed Americans.
>
> For twenty-seven years we have been working to improve the health of the people of India. Now we hear that there is a bill, No. S2878, before the Senate of the United States which, if passed, would permit U. S. drug producers to manufacture and export drugs not approved for use in the United States.
>
> How can we face our Indian friends and medical colleagues if the United States Government passes such a bill which is clearly unethical? How can our Government hold up its head among Third World nations if it enacts such legislation?
>
> As a medical missionary, as a member of the Voluntary Health Association of India and the Christian Medical Association of India, and as a concerned member of the world community, I urge you to do everything in your power to defeat this immoral legislation, Bill No. S2878.
>
> Cordially,
>
> Ronald S. Seaton, M.D.
> Senior Surgeon
>
> cc: Dr. S. Wolfe
> Dr. C. Everett Koop, Surgeon General of the U. S. - personal friend

Warmly,

Ronald S. Seaton, M.D.

cc: Burr Lewis } Presbyterian Men. Mission Fund – contacts
Les Cave } with medical people all over the U.S.
Mira Shiva

VOLUNTARY HEALTH ASSOCIATION OF INDIA
C-14, COMMUNITY CENTRE
SAFDARJUNG DEVELOPMENT AREA
NEW DELHI-110016 INDIA

Telephones 668071
668072
Gram : "VOLHEALTH" NEW DELHI-110016

VHA/[illegible]/ September 17, 1984

Senator Edward Kennedy
The U S Senate
Russel Offices
Room 109
Washington DC 20510
U S A.

Dear Senator Kennedy,

Evidence of the concern felt by health groups over the proposed Bill on export of unapproved drugs is being sent to you.

We can understand the pressure being exerted from the drug Industry lobby but losing the respect and goodwill of the people of the third world countries will not be [illegible] right at all for the present as well as in the long run. Most third world countries have more than enough problems, without new drugs being [illegible].

No one involved in health work or involved with social work, consumer action, education action and development work will accept this Bill without a strong sense of resentment and without protesting.

Perhaps a few years ago before the [illegible] awareness about the relevance of essential drugs and the [illegible] existence of irrational and hazardous [illegible] across this [illegible] it [illegible] have been allowed to be passed [illegible] expression of [illegible].

[illegible] on behalf of our 3000 member health institutions all [illegible] as well as the [illegible] I strongly [illegible] Bill [illegible] there to prevent it.

[illegible],

Yours sincerely,

[illegible]
Director
[illegible] Rational Therapeutics.

AROGYA DAKSHATA MANDAL
SADASHIV PETH
411030.
(India)

आरोग्य दक्षता मंडळ
१९१३, सदाशिव पेठ, पुणे - ४११ ०३०.
सार्वजनिक विश्वस्त संस्था.

फोन : [illegible]

क्र.
दिनांक :- 30 August 1984

Mondale Ferero Election Committee
(through Dr. Arun Phatak, CA 95361)

Sub: U.S.Bill on Export of Hazardous Drugs

Sir,

Bill No. 52678, regarding proposed legislation " to permit US drug producers to manufacture and export drugs that are not approved for use in US " will be shortly introduced in the US Senate.

We strongly feel that this bill is unethical and will directly affect the millions of innocent people of underdeveloped and developing countries.

We are trying to ban drugs viz oxyphenbutazone, analgin, anabolic steroids, estrogen+progesterone [illegible], tetracycline drops and syrup (pediatric use) [illegible] proposed bill is further helping the pharma[illegible] to exploit the suffering humanity.

If you decide to legally allow the [illegible] to manufacture and export dangerous [illegible] disaster. If you, under the pressure [illegible] industry, allow the bill to be passed, it will [illegible] good-will of the third world people.

We therefore earnestly request you to oppose the bill and see that it is not passed. We thank you.

Yours sincerely,

Dr. [illegible]
[illegible] Secretary,
Arogya Dakshata Mandal.

CINI—CHILD IN NEED INSTITUTE
Vill-DAULATPUR, P.O.-AMGACHI
Via-JOKA Pin Code-743512
24 PARGANAS, WEST BENGAL (India)
Telephone 615-531

Our Ref. No. VHAI/20/84

30th August '84

To
Senator Edward.
Russel Offices,
Room 109,
Washington
DC 20510,
U. S. A.

Sub: Proposed legislation to permit US drug producers to manufacture and export of drugs not approved for use in US.

Dear Senator :

We are very grieved to hear that your government is proposing to pass a bill in the US Senate which will allow US drug producers to manufacture and export these drugs not approved for use in your own country. This step as you will realise, will cost the goodwill of the people in India who are now facing most of the brunt of the indiscriminate use of drugs by the manufacturing industry.

This is a retrograd step and it is very unethical to allow the manufacturer in your country to play with the lives of our people and our brothers and sisters in other developing countries. Being very familier with your humane approach and your sensivity to such issues, we hope it will be possible for you and your colleagues to stop this bill from being passed in your senate at all cost. We look forward to a firm action in this matter.

In gratitude.

Sincerely,

Subhanath

Dr. S. N. Chaudhuri
Director

[illegible]

MEDICO FRIEND CIRCLE

Registered Office : 50, L. I. C. Quarters, University Road, Pune - 411016

3.9.1984

To:

Senator Edward Kennedy,
U.S.Senate, Russel Offices,
Room No.109, WASHINGTON DC-20510
U.S.A.

Sir,

Medico Friend Circle is an all-India network of socially conscious doctors and other health-workers, and is quite concerned about the existing irrational drug policy in India. We, in M.F.C., examine the drug-policy in the context of the overall health scene in India. I am writing you to express our deep disturbance over the proposed bill, to be introduced soon (bill No.S2878) about permitting the U.S. drug manufacturers to produce and export drugs not approved for use in U.S.A. This measure is in our view, a retrograde step. If a particular drug is not allowed to be marketed in U.S., how can it be used in a third-world country ? Even if the Government approves such a drug for marketing in India, it may not necessarily mean that the drug is really needed or harmless in our country. In our experience, Government in the third world is influenced by the [illegible] - companies. This is especially true in case of small third world countries. We [illegible] you to exert yourself [illegible] the introduction and [illegible] of the above mentioned [illegible] the senate.

Yours sincerely,

Dr.A.R.PHADKE.
Co-ordinator,
Drug-Cell,
MEDICO FRIEND CIRCLE.

Mr. Ronald Reagan,
President, United States of America,
Washington D.C., U.S.A.

1st September, 1984
Calcutta.

Dear Mr. President,

We beg to draw your kind attention to a bill (No. 52876) which, we understand, is ready to be introduced in the U.S. Senate. The bill, if passed by the Senate, will permit the pharmaceutical companies of your country to manufacture drugs, NOT APPROVED FOR SALE IN U.S.A., for the sole purpose of exporting (those harmful and injurious drugs) to third World countries.

In the past, even in absence of encouragement from the U.S. Government, many multi national companies with head quarters in U.S.A. have utilised the third World countries either as a market for selling substandard and dangerous drugs (disapproved for sale in U.S.A.) at higher prices or to use those countries as field laboratories for trial of new but dangerous drugs, without slightest consideration of their possible ill effects on human lives.

You have reiterated time and again America's intention of upholding human rights whenever and wherever necessary. If the purported bill is allowed to be enacted into a law, it will, in effect, legalise murder of the common and innocent people by the American drug manufacturers in the third World countries. Mr. President, do you not consider it a flagrant violation of human rights ?

We are confident that, you, as the Head of one of the largest democracies of the World, shall not allow the human lives in the third World countries to be endangered merely for financial gain of a few drug manufacturers of your country. We, on behalf of the Indian people, implore you to stop the bill before it is too late.

We earnestly await your reply. With kindest regards,

Your sincerely,

Dr. S. C. Chakraborty, Prsident,
Health Services Association, W. B.
25, Dixon Lane, Calcutta 700 014

Dr. S. B. Chakravorty, President,
Indian Medical Association,
Bengal State Branch,
67 Lenin Sarani, Calcutta 700013

P. Halder

Dr. Parimal Halder, President,
All Bengal Jounir Doctors'
Federation, Kitchen Block,
R. G. Kar Medical College,
1, Khudiram Bose Sarani,
Calcutta-700 004

Dr. Arun Sen, President,
Drug Action Forum, S/3/5,
Sector III, Salt Lake,
Calcutta 700 064

GÖTEBORGS UNIVERSITET
Pediatriska institutionen II

September 1, 1984

Senator Edward M. Kennedy
113 Russell Building
Washington, D.C. 20510 U.S.A.

Dear Senator Kennedy,

I was very surprised to learn that you are expected to vote for the bill to let pharmaceutical manufacturers export drugs that are not approved by the FDA.

Unfortunately, U.S. companies are already producing and marketing dangerous, ineffective and/or useless drugs in other countries. The information that a drug is "Made in the U.S.A." has hitherto been an invaluable guarantee for a certain level of standard. The proposed bill can be of no benefit for the drug consumers, doctors or drug authorities outside the U.S.

Please do not vote for this unnecessary change of a well functioning regulation!

Let me take the opportunity to give you one recent example of unacceptable and unethical - not to say criminal - behaviour of an American drug company.

The enclosed cutting from PHARMA NEWS shows that Wyeth Laboratories in Pakistan has replaced clioquinol with iodoquinol in their drug "Entox".
Obviously the authorities in Pakistan are not aware of the fact that iodoquinol is as neurotoxic as clioquinol.
Clioquinol has caused one of the biggest drug disasters of our time, the so called SMON scandal in Japan, with over 10,000 victims with damage of the nervous system.
It is unbelievable that a big American drug company does not know what they are doing when replacing one neurotoxic substance with another (almost) identical one. Probably the truth is that Wyeth Laboratories cynically has misused the ignorance of the authorities in Pakistan concerning the toxicology of the halogenated hydroxyquinolines.

Again, I urge you not to vote against common sense and the interests of millions of defensless people outside the U.S.

Very truly yours,

Olle Hansson, M.D.
Head of the Neuropediatric Section

Postadress Barnklinikerna
Östra sjukhuset
416 85 GÖTEBORG

Telefon
031 - 37 40 00

Postal address University of Göteborg
Dept. of Pediatrics II
East Hospital
S-416 85 GÖTEBORG
Sweden

Fortnightly
PHARMA NEWS
Karachi
15-31 August, 1984

Clioquinol free reformulated entox now available

Pharma News Report

The sudden vacuum of anti-diarrheal products created as a result of ban on clioquinol by Ministry of Health in February, 1984 will be considerably relieved by availability of clioquinol free Wyeth's Entox.

The green Entox tablet was one of the most well-known and prescribed antidiarrhoeal in the country till its production was stopped by Wyeth.,

Entox is a combination product containing Activated Attapulgite, a potent adsorbent but suffered because its other ingredients, clioquinol, alleged to have harmful effects. After an absence of about 5 months, Entox is now available wherein clioquinol has been replaced with Di-iadohydroxiquinoline (also called Iodoquinol).

Entox was being exported to many African countries and to the countries in the Far East, earning valuable foreign exchange. It is expected that now the reformulated form will be supplied in due course.

(Institut de Pharmacologie
de l'Université de Lausanne
Rue du Bugnon 21
Lausanne
Switzerland

October 3, 1984

Senator Edward M. KENNEDY
113 Russell Building

Washington, D. C. 20510
U.S.A.

Same was sent to [illegible]

Senator,

Friends and colleagues in the United States draw my attention to a bill to be discussed before the Senate which would authorize the export of drugs, i.e. medicines, not authorized for sale in the United States to other countries (comprising drugs which having been authorized have been withdrawn). My friends in the States advise me that you might vote in favor of this bill. It is the purpose of the present letter to draw your attention to the fact that in view of your reputation as a defensor of consumers' rights and of the rights and interests of people in the Third World, your vote in favor of such a bill would greatly deceive all those who, in the whole world, try to obtain legislation which would protect the health and the survival in the countries without drug industry, i.e. in what is commonly called the Third World.

All highly developed countries which develop, produce and sell drugs for medical use are faced with the fact that among a hundred newly developed molecules tested for possible medical use, only one to two finally become "medicines" effective for certain therapeutic purposes and not exposing the consumers to much danger. Another 5 to [illegible] among the hundred drugs primarily tested come out to be potentially useful, but are never actually used either in hospitals or in free practice because they present dangers to the health of the treated persons. In some countries, as in the United States, such drugs are not admitted for sale to the public in the country of production. On the other hand, even among drugs which have been given a permission for general use, some prove to be dangerous, i.e. in the course of a few years of application to man, they produce potentially dangerous side effects. Such drugs, in most countries, are withdrawn from the domestic market.

This leaves the industry with sometimes huge amounts of drugs which cannot be sold anymore domestically. Producers tend to export such potentially harmful drugs to Third World countries which usually do not have a legislation protecting their inhabitants against harmful drugs or, even if they have such legislation, do react very slowly when a drug has been banned in another country. Such exports constitute a major danger to the health of the population of these countries, since drugs which are dangerous even for well-fed and usually well-cared-for Americans or Europeans may prove to be much more dangerous to undernourished people in the Third World who, furthermore, may suffer from chronic parasitic or microbial diseases.

Therefore, in practically all highly developed countries of the Western world and even in some countries of the Communist Block, medical experts and private organizations, comprising Consumers' Unions try to obtain a legislation which would prevent the export of medical drugs not authorized for sale within any given country to other countries. In their attempts to obtain such legislation, those who defend the interests to a sane life for inhabitants of the Third World tend to vote as an example of good legislation the laws presently applied in the United States which would be abolished if the new bill was accepted by the Congress. Now, it is a primary truth that a ban of exports from any country only becomes effective if it is applied not only by the country itself but also by other countries. The fight for a legislation modelled on the present legal situation in the United States is, therefore, of primary interest for millions of people and for those who try to defend them.

For all these reasons and in view of your great prestige, not only within the United States, I urge you not to deceive those who may be influenced by your action, and to fight a bill which would put the United States in the situation of unfortunately so many countries whose legislation primarily defends domestic producers and exporters' interests.

Looking forward to better news I am

Yours very sincerely,

G. P

Georges PETERS, M. D.
Professor and Chairman

CGSI

20th Sep. 1984

To,
Senator Edward Kennedy,
The US Senate,
Russell Offices,
Room 109,
Washington DC 20510,
U.S.A.

Dear Senator Kennedy,

We have learnt from a friend that a Bill No 52878 which aims to permit the export of "Food and Drug Administration(FDA) unapproved drugs" from US is nearing the end of the committee stage in the senate. We have gone through the summary of draft legislation (10/4) permitting US manufacturer, an export of drugs not approved for US use. We are pained to learn of such a restrograde step by a democrati Government like yours. Many people in your country, including your late brother John F Kennedy, have been protecting human rights universally. But now it seems that the concept of 'Profit at any cost is being encouraged in preference to the basic human values. If FDA in your country considers a drug unsafe for use in humanbeings in your country, how does your Government justifies its use in humanbeings in other countries. This shows that either your Government itself does not have faith in the creditibility of its own FDA or your Government is not concerned with the safety of humanbeings in other countries.

We sincerely hope that you will ~~mmt~~ act in the interest of humanbeings all over on our planet and shall not allow the US senate to pas this Bill. Thereby you shall also reinforce the creditibility of your nation.

Yours faithfully,

Dr. PAWAN SUREKA,
M.D.; D.C.H.; F.C.P.S.;M.N.A.M.S.
CHAIRMAN,MEDICAL COMMITTEE
Consumer Guidance Society of India.

Biotech Firm Forms Joint Venture in Singapore

By Nell Henderson
Washington Post Staff Writer

Biotech Research Laboratories Inc. has formed a joint venture to establish a research and manufacturing facility in Singapore, hoping to enter East Asian markets with economical products suited to that region's medical needs.

"We have had substantial interest from the Far East in our products, but because of the strong dollar, the actual market has been limited," said Thomas M. Li, president of the Rockville biotechnology firm. "This new company will enable us to take advantage of a market that encompasses the majority of the world's people in a price-competitive manner."

The new company, Diagnostic Biotechnology Ltd., will concentrate on products that meet medical needs that are more prevalent in Asia, while Biotech Research focuses on products for the U.S. market, Li said.

Biotech Research has developed a line of 35 monoclonal antibodies, biological substances used as research tools and in viral diagnostic tests. One of the firm's most successful products, developed jointly with E.I. du Pont de Nemours & Co., is a test to detect exposure to the virus believed to cause Acquired Immune Deficiency Syndrome (AIDS).

Some of Biotech Research's products are used to diagnose viruses linked to diseases that are more common in Asia than in the United States, such as one type of leukemia and certain cancers. The Singapore venture will provide a low-cost vehicle for getting those products to the Asian market, while broadening the revenue base of a 12-year-old firm moving from research to production.

Biotech Research lost $1 million in 1984 on revenue of almost $3 million, compared with a loss of $1.2 million on revenue of $1.9 million the year before. Product sales increased 482 percent in 1984, to $797,000, while client-sponsored contract revenue increased 24 percent to $2.2 million.

The new Singapore-based firm was formed with a group of Singapore investors who will provide $4.5 million in start-up capital. Biotech Research Labs will own 25 percent, or 2.5 million of the initial 10 million shares of common stock, and will provide technical training and assistance, the company said.

Biotech Research's scientific director, Robert C.Y. Ting, will be a member of the new firm's board of directors.

The facility, which should begin operations this fall, initially will produce Biotech Research products for sale in Asia. Biotech Research scientists also will train Asian scientists in laboratory techniques to be used to develop new products for that market, Li said. Biotech Research will continue product manufacturing in Rockville for the U.S. market, he added, citing the benefits of low shipping costs and proximity to federal regulatory agencies.

Diagnostic Biotechnology will have several financial advantages in Singapore. The company has been granted "pioneer" status, which exempts it from corporate taxes for eight years. Singapore's trade treaties allow goods to be exported to many Asian and some European countries duty-free. Shipping and labor costs also will be lower.

"It's not cost-competitive to produce here for their market," Li said.

PHOTO BY FRANK JOHNSTON—THE WASHINGTON

Thomas Li, president of Biotech Research Lab

Li said there is no danger that Biotech Research will be giving away technical advantages to potential competitors. "We will be using very standard technology," he said, referring to the method of fusing special cells to produce a stream of pure antibodies, called monoclonal antibodies. "It's in all the scientific journals."

Washington Post Washington Business Section p. 3 7/1/85

The **Chairman**. Ms. Drabble.

Ms. **Drabble**. Thank you. I would like to briefly discuss six specific defects with the recent Genentech proposal. First, the Genentech proposal fails to include antibiotics in its coverage. If anything, antibiotics should be brought under the current law of prohibition against exports. It makes no sense to have a meager set of restrictions for the export of unapproved drugs and no restrictions at all for the export of antibiotics. In fact, under current law unapproved antibiotics can even be exported if they are unadulterated or misbranded.

Second, as discussed by Dr. Wolfe, reliance on Western European drug approval systems provide little consumer protection because of the serious mistakes those systems have made. In addition, the Genentech proposal provides no definition of an adequate drug approval system and also fails to require that those drug approval systems be comparable to our system.

Third, the Genentech bill contains no safeguards to prevent reshipment to the Third World and that issue has been quite thoroughly discussed. Because of that, we do not feel that it offers a real compromise on the issue, it is just a cosmetic change that would make Western Europe a way station for drugs on their way to other countries.

Fourth, the Genentech bill allows approval of export of drugs which have been voluntarily withdrawn from the U.S. market, since the FDA often permits companies to take drugs off the market voluntarily. This is really a significant loophole. Also the bill contains other procedural defects. It allows export without affirmative FDA approval. It provides no opportunity for the public to object to the export of an unapproved drug, and it also fails to give FDA discretionary authority to disapprove exports or to cancel export authority because of safety problems.

Fifth, the Genentech bill fails to require companies that want to export unapproved drugs to provide FDA with sufficient information in order to make a reasonable decision. How can FDA exercise even limited veto power if it does not have information on which to base its decision. FDA is given no new power over industry's export practices and the Agency cannot even revoke export authority if the drug is banned in one of the listed countries, thus approval in a listed country triggers export of an unapproved drug but disapproval in one of the listed countries does not trigger disapproval.

Sixth, a drug company need only file an application for an investigational new drug exemption. This is a meaningless restriction, since it does not require that the drug eventually receive full U.S. approval. The drug companies argue that they only want to export drugs which are going through the U.S. process, but under the bill they need never submit and need never complete an NDA application. They probably will not in many instances, because only 10 percent of the drugs that are in the IND process ever make it to phase III clinical trials, let alone an NDA application, thus triggering export with an IND filing provides little safety, particularly since the drug is given to very few patients at this stage.

I would also like to comment just briefly on the argument made by the biotech companies about the transfer of technology. What the industry fails to acknowledge is that the real reasons for technology transfer are not any restrictions on drug exports. The real reasons why biotech companies engage in joint ventures are a number of other reasons.

First, they need foreign capital because the flow of U.S. capital to biotech companies has slowed and so they need to make those joint ventures. Second, foreign countries have engineering personnel and production facilities that are not available in the United States. Third, foreign partnerships allow U.S. companies access to markets that it could not otherwise get into because of the desire of foreign countries to develop their own exports. In recent Washington Post articles, even Du Pont was saying that it needed to have joint venture in Japan because otherwise it simply could not be successful in the Japanese markets.

Also American biotech companies gain scientific knowledge from joint ventures that they would not otherwise get, so in this way the technology transfer goes both ways. We also get information.

Also the largest technology transfer occurs through scientific journals and conferences and the drug export bill does absolutely nothing about this. Also the underlying premise that biotech products are approved first in Europe may also be inaccurate. In the Commerce Department report that Dr. Wolfe was referring to, they said that the United States has the least restrictive recombinant DNA guidelines, and so it is not even necessarily true that those products will be approved first in the United States.

We would be glad to answer any questions you might have.

Thank you.

The CHAIRMAN. Well, thank you. Thank you both.

I have to state that while our points of disagreement are many, there are a couple I feel like I really just have to comment on.

First, Dr. Wolfe, you use a double standard slogan, and many who are familiar with this issue I think just do not look beyond this level. I hope that our other testimony today has demonstrated what we are really talking about is not a double standard in the pejorative sense but a different standard, a different determination of risk versus benefits which is a legitimate, even a necessary concept, at least from my point of view.

Second, you again claim that if S. 2878 were to pass, foreign consumers would be subjected to the least common denominator of protection since they could have access to the worst drugs approved by any country.

I think this is simply illogical when we realize that, right now, foreign consumers have access to any drug from France or Germany or anywhere, for that matter, whether or not it has been approved there.

I am not advocating that they should be exposed to additional drugs as you imply. The drugs which would be allowed under S. 2878 are a subset of drugs which are already available to foreign consumers, a subset which will have to meet numerous standards if this bill is passed.

Dr. Wolfe, in your testimony before the committee last year, you pointed out:

> The existence of different conditions abroad—different diseases, nutrition, sanitation, education, availability and quality of water, availability of health personnel

and facilities—could mean that a drug acceptable for use here will be harmful or useless elsewhere.

Now, is not the converse also true, that because of differing conditions, a drug unacceptable for use here may be very helpful abroad?

Dr. **Wolfe**. In the discussion of the double standard, I agree that whereas some of these drugs might be available because they may be made somewhere else and already exported to other countries, the question is do we want to make drugs here on American soil with made in U.S.A. labels that we would not use at home. It is a double standard, call it a different standard, I mean I do not think there is any difference. The point is we would enter——

The **Chairman**. They may be drugs we will use at home.

Dr. **Wolfe**. Pardon?

The **Chairman**. These may be drugs we will use at home. They are just not approved by the FDA.

Dr. **Wolfe**. Well, the bulk of—I mean as Ms. Drabble pointed out, the bulk of drugs that would qualify here will never get approved in this country, the standard is so low. I mean one out of a hundred or two out of a hundred drugs that go into clinical trials ever get approved. They would not eventually get approved here.

The second point you mention is that we would only be talking about a subset of drugs that are already available. I think that the impact of this bill, as the industries stated this morning, was really not on drugs already available because drugs that are already being manufactured by an American company called Merck in a foreign country are going to continue to be manufactured abroad. They are really talking in the future about drugs that have not yet been approved, not a subset of drugs that are already available. And that really is a different story.

The third thing you mentioned, namely the issue of drugs that do not have an advantageous benefit risk ratio here but might in other countries, that is really, as it has become known, the tropical disease exception. I think that we have abundant ability under existing authority, it is evidenced under the orphan drug thing, and it is very comparable. Orphan drugs are drugs that really do not affect that many Americans, but a special case needs to be made to speed them up, get them for the people who need them even though the risk benefit ratio may be different than that of an antihistamine.

The same applies to the tropical disease drugs. And I think again the case of this major drug, praziquantel, made by Bayer and then licensed to Miles in this country, is the best evidence that we do not need new legislation to accomplish this issue of drugs that have different benefit risk ratios in foreign countries than they do here. We do not have schistosomiasis here, really, other than in the State Department people who may get it in other countries. But it got through smoothly. And I am very encouraged by this two-track system, with a couple of exceptions, that the FDA has been working on in the last 4 or 5 years. The drugs that really look important, whether they are for foreign or domestic use, get sped up in their approval. The ones that are just "me too" get slowed down. And I think that is fair, and it gets the most important drugs to market first. And I think that that will continue.

I would be very surprised to see any example of another schistosomiasis drug for which approval had been sought but denied. Remember, one of the things that Mr. Lucas said is that it was the USAID that encouraged Miles to file the NDA. The FDA cannot approve a drug until the company has asked for approval. And I wonder why, for example, if the drug had been approved in West Germany in 1980, someone did not even seek approval in the United States until 1981, and it got quickly approved once approval was sought. I think it was 11½ or 12 months later.

I think that there is a remedy for that third problem. It is a serious problem. But I think the main problem with the tropical disease issue is there is not enough money to buy the praziquantel and other comparable drugs for the Third World countries. The Africare group has done, I think, an important study financed by the drug industry looking at the whole question of availability of drugs. And most of them we are talking about are the penicillins and the very needed essential drugs, the availability of these drugs in the African countries. That is a question of money; it is not a question of the approval by the FDA. Most of the drugs, if not all of them, are already approved by the FDA.

The CHAIRMAN. It seems to me that your bottom line is that allowing the export from the United States of unapproved drugs is harmful to foreign consumers.

But, really, do you have any evidence at all that if export were allowed along the lines set forth in last year's bill, there would be any increase in the incidence of mortality or illness among foreign consumers? Do you have any evidence at all?

Dr. WOLFE. The evidence was the evidence that I cited this morning, namely the six drugs that just in one country alone had been banned. The evidence is that all the people killed by those six drugs, all the 15,000 injured, would have been injured by something made in the United States instead of something made somewhere else.

The CHAIRMAN. I have heard that before.

All of your examples——

Dr. WOLFE. You do not disagree with that though?

The CHAIRMAN. Now, wait a minute. All of your examples are drawn from cases occurring overseas right now despite the current ban on U.S. exports.

Dr. WOLFE. That is right.

The CHAIRMAN. They simply demonstrate that the ban does not protect foreign consumers. And I cannot understand—I really cannot understand how partially lifting that ban in a responsible way will decrease protection that they do not have in the first place.

Indeed, if they were to choose to buy an unapproved drug produced in the United States under last year's bill instead of a similar drug manufactured elsewhere, they would, in all likelihood, be receiving a better product because of the protections built into that proposal, including manufacturing, testing and labeling protections.

Now, let me just put this question to you, Dr. Wolfe. If we take a villager in Chad who is going to take a drug not yet approved in the United States, would you rather have him purchase a version produced abroad under few, if any, requirements, or would you rather have him purchase the version manufactured in this country under the restrictions and the requirements of last year's bill?

Dr. WOLFE. Well, I do not think that is the issue addressed by this legislation. It is a matter of——

The CHAIRMAN. It sure is.

Dr. WOLFE. The six drugs that I cited were all approved and manufactured in West Germany, the United Kingdom countries which you yourself say——

The CHAIRMAN. Whether perhaps or not they are going to be able to be distributed.

Dr. WOLFE. Excuse me. You say that those countries have comparable standards to the United States. I do not think they do which is why they were approved there and not here.

It is a matter of which country is responsible for killing and injuring people, the United States for having made the drug here, or another country. It would be better to have neither country responsible. But we certainly do not want to add the United States to the list of countries responsible for these needless deaths and injuries.

The CHAIRMAN. Well, I have got to admit, my original question, I do not think you have answered.

Is there going to be any increase in mortality or illness among foreign consumers if we pass this bill?

Dr. WOLFE. We do not know because we cannot tell, for example, whether or not if they were made in the United States there would be a much greater worldwide distribution. There is no way of answering that because, as you said, as the industry said, this only applies to drugs really that have not yet been approved. We do not know what is going to happen. We do not know, for example, whether Merck, an American based company, if they were allowed to export unapproved drugs, would cause a much wider worldwide distribution of the drug than if it were being manufactured in Britain or in West Germany.

So the answer is we do not know.

The CHAIRMAN. Now, Mr. Wolfe, in the United Nations General Assembly resolution 37-137 of March 3, 1983, the United Nations addressed policy on the export of both unapproved and banned materials, and let me quote:

> For products that have been banned from domestic consumption and/or sale because they have been judged to endanger health and the environment should be sold abroad by companies, corporations or individuals only when a request for such products is received from an importing country or when the consumption of such products is officially permitted in the importing country.

Now, I might note here that the bill I introduced last year would not have allowed the export of banned materials at all. But let me just continue the quote:

> All countries that have severely restricted or have not approved the domestic consumption and/or sale of specific products, in particular pharmaceuticals and pesticides, should make available full information on these products with a view to safeguarding the health and environment of the importing country, including clear labeling in a language acceptable to the importing country.

Thus, under the policy endorsed in this resolution, unapproved drugs would be handled under an information sharing system much less stringent than the protections in last year's bill on not-yet-approved drugs.

This United Nations resolution was adopted by 146 countries voting in favor.

Now, my question is, Does Public Citizen disagree with the position taken by virtually all of the developing nations?

Dr. Wolfe. Well, I mean for some countries, that would be an improvement over what is going on now. For other countries, it would not make any difference because the current policies, these are not binding on anyone.

I would like to quote——

The Chairman. My point is the bill provides better protections than they have even asked for in their resolution, which was a well considered resolution.

Dr. Wolfe. Well, I disagree. I would like to quote, the European Parliament last year adopted a resolution which said, "The protection of European consumers against imports into the EC, of products declared unfit for consumption by U.S. legislation." They are opposed to that. So that is the European countries, the very ones who are supposedly having the adequate system that we could export——

The Chairman. But I am talking about the developing countries.

Dr. Wolfe. Excuse me?

The Chairman. I am talking about the developing countries, 146 of which voted for that particular resolution.

Dr. Wolfe. Well, as I said——

The Chairman. I am not talking about Europe.

Dr. Wolfe [continuing]. For some countries, that would be an improvement over the reckless way that things go on now.

But, again, we can only affect here in this country what happens on American soil. We really have no control, fortunately or unfortunately, over what is manufactured elsewhere. This legislation does not touch——

The Chairman. I think we would if we had this legislation because if we ban it here, it could not be sold elsewhere.

Dr. Wolfe. If we ban it——

The Chairman. To the country by the company.

Dr. Wolfe. As it is now, that is the case. There is no difference. We are not now allowed to sell drugs which are banned in the United States elsewhere. That is not any change at all.

The Chairman. Are you familiar with Health Action International?

Dr. Wolfe. Yes, I am.

The Chairman. I understand that it is a network, a coalition of groups from many countries which lobbies intensively at the World Health Assemblies and other national and international health meetings on issues with impact on the developing world.

I~~s your~~ organization, or the organizations you are affiliated with, are any of the NADER organizations, are they affiliated with HAI?

Dr. Wolfe. We are not a member of or affiliated.

I read a telegram that HAI sent as part of my testimony, but that is because they knew——

The Chairman. There is no affiliation?

Dr. Wolfe. Excuse me?

The CHAIRMAN. There is no affiliation?

Dr. WOLFE. We are not a member of HAI or anything like that, no.

The CHAIRMAN. OK.

Now, your testimony shows you are aware of opposition to S. 2878 which, of course, HAI attempted to generate abroad.

Let me ask you this. Did you not join with it in writing senior World Health Organization officials in a campaign to obtain the dismissal or disavowal of Dr. John Dunne, the senior pharmaceutical officer of WHO after he gave his testimony last year in the House, which was viewed as favorable to the relaxation of the U.S. ban on unapproved drugs? And to your knowledge, has WHO repudiated Dr. Dunne's testimony?

Dr. WOLFE. Well, I and a number of other people, including people involved in HAI and people who have nothing to do with HAI, wrote letters objecting to the idea that you, amongst others, believed that his testimony was, one, speaking for all of the WHO, and, two, amounted to a strong endorsement as the PMA——

The CHAIRMAN. You tried to get him dismissed.

Dr. WOLFE. Excuse me. I did not try and get his—there is nothing in my letter trying to get him dismissed. I tried to get the WHO in the letter to read the letter—you know, I think you obviously have a copy of it—all I asked for was for the WHO to consider separating themselves from his viewpoint, not to get him dismissed, to simply say does this——

The CHAIRMAN. The HAI tried to get him dismissed.

Dr. WOLFE. Well, they may have. I am not aware of that. I do not have that correspondence All I asked for was does this represent WHO's viewpoint, and the response indicated that it really did not in the sense that they did not endorse the legislation as the PMA had claimed they did and as you did when I debated you on the Today show. You, I think, had the idea that Dr. Dunne was actually endorsing this legislation. I think at least WHO's reading of Dr. Dunne's testimony and their own viewpoint was that it's much more limited than you felt.

The CHAIRMAN. It inferred that WHO stood behind Dunne on his testimony given.

Dr. WOLFE. Well, the letter that I got did not say that the testimony given was an endorsement of your legislation, but it did not endorse your legislation clearly.

The CHAIRMAN. I do not think I counted it as an endorsement of legislation. I did say it was——

Dr. WOLFE. The PMA did. No, the PMA did.

The CHAIRMAN. I said it was an endorsement of the concept that we were talking about.

Dr. WOLFE. Well, the PMA specifically said that it was an endorsement, and I do not think that they really endorsed the concept. I think that they specifically are in favor of the ways being found for the so-called tropical disease drugs to get to other countries, but not as broad as your legislation would have it.

The CHAIRMAN. Well, let's put WHO's reply into the record. Do you have a copy of that?

Dr. WOLFE. Pardon?

The CHAIRMAN. Do you have a copy of that reply?

Dr. **Wolfe**. I am sure I can find one.

The **Chairman**. Will you provide that for the record, please?

Dr. **Wolfe**. Yes; I will.

The **Chairman**. OK. Let's make that part of the record at this point.

[The material referred to follows:]

UNAPPROVED DRUGS #995

Public Citizen

Congress Watch • Critical Mass Energy Project • Health Research Group • Litigation Group • Tax Reform Group

December 21, 1984

Dr. Halfdan Mahler
Director General
World Health Organization
1211 Geneva 27
Switzerland

Dear Dr. Mahler:

On July 27, 1984 Dr. John Dunne, Chief of the Pharmaceuticals Unit of the World Health Organization (WHO), in testimony before the U.S. House of Representatives Health Subcommittee, endorsed proposed amendments to the Food, Drug, and Cosmetic Act that would permit drugs which have not met United States standards for safety and efficacy to be shipped overseas. Public Citizen's Health Research Group, a public interest organization, urges you to renounce immediately Dr. Dunne's apparently unauthorized testimony before the subcommittee as not representing the position of WHO. Indeed, these amendments are in direct conflict with the expressed purpose of WHO's Action Programme on Essential Drugs and Vaccines, which seeks to eliminate the use of inferior, unnecessary, and ineffective drugs. Dr. Dunne's ill-advised statements have cast WHO as an unwitting endorser of the proposed legislation.

Health Research Group has long opposed legislation which would permit the export to developing countries or elsewhere of drugs deemed unfit for consumption by the American public. We oppose a double standard whereby the lives of foreigners would somehow be considered less worthy of protection than those of U.S. citizens. We enclose a copy of our testimony at the House hearing, which outlines our position in more detail.

In his written testimony Dr. Dunne asserted that the Food, Drug, and Cosmetic Act should not prevent the dissemination of "valuable medicines where they are most urgently needed." Dr. Dunne, therefore, completely ignored the fact that the vast majority of drugs manufactured for export purposes only, far from being "valuable," would be unsafe, ineffective, and inferior to those approved for the U.S. market. We do not believe that this position is consistent with WHO's aims.

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Drugs of proven therapeutic value would already have been subjected to the rigorous testing procedures required in the U.S. and are eligible for export under current law. Biltricide, for example, a drug used in the treatment of schistosomiasis, was recently approved by the U.S. Food and Drug Administration despite the fact that the disease is a relatively minor public health concern in this country.

Dr. Dunne's oral testimony, partly in response to questions posed by Congressman Henry Waxman who chaired the hearing, went considerably further than his written statement in endorsing the proposed amendments:

*Dr. Dunne answered "firmly and affirmatively" the question of whether there exists or might in the future exist a need for "developing countries to import pharmaceutical products that are not approved for domestic use within the U.S.A."

*Later in his oral testimony, Congressman Waxman tried to pin down Dr. Dunne's position. Rep. Waxman asked Dr. Dunne whether it was his position that "if a country wants to import a drug, they should be permitted to import it and the United States shouldn't stop them from receiving a drug that was manufactured in this country, notwithstanding the fact that the FDA won't allow it to be used here?" Dr. Dunne responded, "In general, yes," but went on to describe an "extreme situation" where FDA prevention of export might well be appropriate.

*Asked by Rep. Waxman whether he felt that "there is adequate information, [other countries] ought to make the decision for themselves, [and] the United States shouldn't make it for them?" he replied: "I think so ..."

Sources with the highest authority within WHO contend that Dr. Dunne's statements do not accurately represent those of your organization. Unfortunately, absent a repudiation by WHO, some have understandably continued to depict Dr. Dunne's testimony as WHO endorsement of the amendments; a formal renouncement of Dr. Dunne's testimony as being inconsistent with WHO's philosophy and programs is therefore imperative.

Senator Orrin Hatch, a sponsor of the proposed amendments, has on several occasions cited WHO endorsement of his initiative. He has done so on the NBC television program "The Today Show" (August 29, 1984) as well as in letters to various national consumer organizations.

Food, Drug, and Cosmetic Reports ("F-D-C Reports", October 8, 1984), a weekly trade newspaper covering drug-related issues, claims that "PMA [United States Pharmaceutical Manufacturers Association] and WHO are together in support for easing U.S. export restrictions," while the PMA newsletter described WHO's Dr. Dunne as "the staunchest, most unqualified proponent of export of unapproved drugs" at the House hearing.

The PMA has declared that the export bill will be a "high priority" for them in the upcoming legislative session. It is likely that the bill will be introduced for the upcoming legislative session within weeks; PMA can be expected to lobby vigorously for this bill, prominently touting WHO's purported endorsement. In view of the prominent role the non-existent WHO endorsement has already played in the debate, we urge you to publicly clarify WHO's position on the issue and to disassociate your organization from Dr. Dunne's personal beliefs. With WHO's credibility as the leader in global health promotion at stake, we have the utmost confidence that you will act rapidly to reverse the misperception of WHO's stance on an issue of such great import to consumers worldwide.

Yours sincerely,

Sidney M. Wolfe, M.D.
Director

Peter Lurie

Peter Lurie
Researcher

cc: Senator Orrin Hatch
Senator Edward Kennedy
Senator Howard Metzenbaum
Represenatative Henry Waxman

DGO

Dr Sidney M. Wolfe
Director
Mr Peter Lurie
Researcher
Public Citizen
Health Research Group
2000 P Street N.W.
Washington, D.C. 20036

Geneva, 15 January 1985

Dear Sirs,

The Director-General has requested me to reply to your letter to him dated 21 December 1984 concerning proposals under consideration in the USA Congress to amend the Food, Drug and Cosmetic Act concerning the export of drugs.

In order to clarify WHO's official position on matters such as these I should like to point out that WHO is an Organization of Member States. Obviously, they have not considered the proposed amendments to the US Congress Act; that would be outside the constitutional mandate of the Organization. They have, however, through the Organization's governing bodies, taken a firm stand on the issues concerned in two complementary ways.

Through its Programme of Drug Quality, Safety and Efficacy WHO provides objective information on drugs, their uses and abuses, their indications and contra-indications, and their adverse effects. One of the instruments for
... doing that is the Drug Information Bulletin, of which I attach a typical copy. Moreover, WHO has introduced a Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce in which to date 107
... Member States are participating. I am attaching a copy of this too. In 1984, the Third International Conference of Drug Regulatory Authorities, which is cosponsored by WHO, attracted drug regulators from 56 countries, over half of them from developing countries. This facilitated a free exchange of views between developing and developed countries on drug regulatory issues, including the implementation of relevant resolutions of the United Nations System.

Moreover, WHO has laid particular emphasis in recent years on strengthening the capacity of developing countries to absorb and use the information disseminated to them with a view to enabling them to decide by themselves what drugs to permit - whether made available through importation or through local production - and how to regulate accordingly. This is being done in keeping with WHO's policy of fostering national self-reliance on all

cc: Director-General

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... ENCLs: (3) Documents A35/7; PDT/DI/84.1; PHARM/82.4 Rev.1

health matters. I should add in this connection that the countries that sponsored the resolutions of the United Nations General Assembly concerning protection against products harmful to health and the environment insisted on their rights to import as they felt necessary. To give an example of WHO's attitude to this, some years ago WHO's Executive Board studied the place of DDT in operations against malaria and other vector-borne diseases and reached the conclusion that for developing countries the use of this insecticide to combat the disease was justified on risk/benefit grounds, taking into account the cost of alternatives, even if a number of more affluent countries that had eradicated malaria had placed severe restrictions on DDT.

The second way in which WHO has taken a firm stand on the issues concerned is by establishing the Programme of Essential Drugs and Vaccines, which is steadily gaining ground. The World Health Assembly adopted the main lines of action for implementing that Programme, a copy of which is attached. As you can see, the Health Assembly laid particular emphasis on the development by countries of their own essential drugs programmes and indicated the main components of these (see section IV in particular). Countries following faithfully those lines of action, starting with the selection of drugs that are appropriate to their needs and including all the managerial, educational, economic and legislative action required, would be in a very solid position to resist any undesirable external influences. WHO is cooperating very actively with many of its Member States to set up and maintain such programmes. It is doing so in the context of the stark reality that the most urgent problem today is how to get essential drugs to the 90 percent of people in the developing countries who have little or no access to them. I am referring not even to the two-hundred-odd drugs on WHO's model list of essential drugs but to the mere 25-30 drugs acutely required for primary health care, including antibiotics, drugs for tropical diseases, tuberculosis and the like, in addition to analgesics and substances for skin conditions such as scabies.

Turning to Dr Dunne's statement before the Health Subcommittee of the US House of Representatives, as further reading of it will show he made no recommendations with respect to the proposed amendments to the Act in question, but rather presented information on prevailing practices with respect to issues relevant to those amendments. Thus, he stated that the major drug exporting countries with the exception of the USA exempt drugs intended for export from controls applied to drugs destined for domestic use; this is a statement of fact, not a condonation of it.

In exceptional circumstances, certain drugs, for example drugs required to treat certain tropical diseases, are required by some countries that are not in a position to manufacture them, and are not required by other countries that are in a position to do so. To give you some examples, the following substances are, to the best of my knowledge, "unapproved" in the USA, although included in WHO's model list of essential drugs: clofazimine and protionamide for leprosy; dehydroemetine and diloxanide for amoebiasis; melarsoprol and nifurtimox for trypanosomiasis; metrifonate for schistosomiasis; sodium stibogluconate for leishmaniasis and suramin sodium for filariasis as well as trypanosomiasis. Under these exceptional circumstances, it would be a case of countries in need cutting off their nose to spite their face if they did not import the drug concerned merely because it was not being used in the exporting country. Moreover, it would be a strange ethic to forbid the export of a drug needed in another country just because it was not needed in the country that was capable of manufacturing it.

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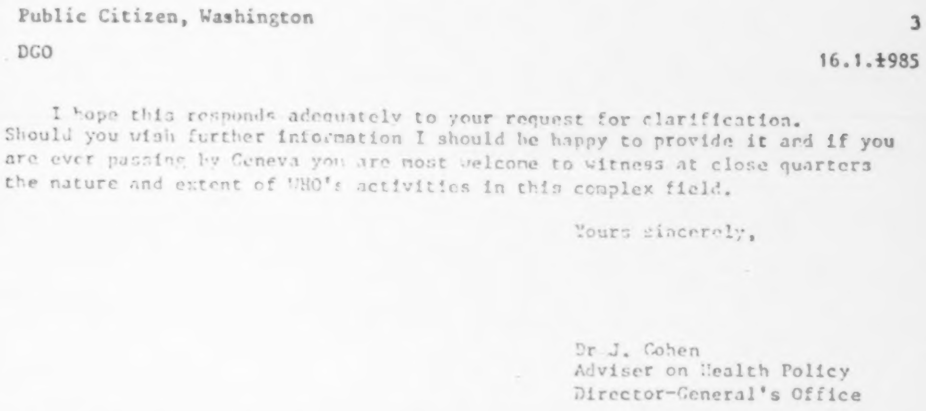

Public Citizen, Washington 3

DGO 16.1.1985

I hope this responds adequately to your request for clarification. Should you wish further information I should be happy to provide it and if you are ever passing by Geneva you are most welcome to witness at close quarters the nature and extent of WHO's activities in this complex field.

Yours sincerely,

Dr J. Cohen
Adviser on Health Policy
Director-General's Office

The CHAIRMAN. In a letter to Dr. Cohen, Assistant Director General, WHO, which formed part of this campaign, Virginia Beardshaw, the lead HAI official on this issue, conceded that Dr. Cohen's point expressed in his letter to her that "The right of all countries to import drugs as they see fit" is "well taken."

The CHAIRMAN. Now, does Public Citizen disagree with this statement from HAI's Coordinator for Pharmaceutical Issues?

Dr. WOLFE. I have not seen the full statement so I really cannot say whether I——

The CHAIRMAN. Well, assuming that the statement that I just gave is true, do you disagree with it?

Dr. WOLFE. I disagree with the right of countries to import any drug that they want in the world. Is that what your question is?

The CHAIRMAN. Well, the HAI official conceded Dr. Cohen's point expressed in his letter to her that the right of all countries to import drugs as they see fit is well taken.

Do you disagree with that concept?

Dr. WOLFE. I do.

The CHAIRMAN. OK.

Dr. WOLFE. That is what our testimony is on.

The CHAIRMAN. OK.

You know, there is a broad consensus among health authorities that the developed countries need to take into account their particular unique circumstances in deciding whether drugs are appropriate for use in their countries.

Now, your motivating fear, it seems to me, to be that when it comes to unapproved drugs, they will make the wrong decisions. So they should not be allowed to decide.

Now, am I correct, and if I am, do you not think that is a little bit of a colonial approach to Third World countries by you and your organization?

Dr. WOLFE. No; you are not correct, because I pointed out that within existing authority it is possible to provide Third World countries with drugs that are judged safe and effective by American standards and which are needed for diseases such as schistosomiasis. We do not need any new laws for that.

The CHAIRMAN. Well, what about their conditions and their standards?

Dr. **Wolfe**. Give an example of a condition. I mean other than—schistosomiasis. Schistosomiasis, I think, is a good example. That is why it was used as the main example by Mr. Lucas. I mean if you have others, I am sure that the same expedited FDA review if the drug is safe and effective can be found, we do not need to export an unapproved drug.

The willingness of foreign countries, many of them, to use a drug such as Biltricide is enhanced when it is approved in the United States. It is not decreased.

The **Chairman**. Well, I just cite your own conditions from your own statement abroad, different diseases, nutrition, sanitation, education, availability and quality of water, availability of health personnel facilities, you know, all of those, are——

Dr. **Wolfe**. And all of those can be met by approving the drug here in an expedited fashion as was done.

The **Chairman**. How does FDA know what all those conditions are? Why should not the country be able to make that determination?

Dr. **Wolfe**. The answer is that in the new drug application for Biltricide, for example, all of those conditions were made quite clear because the safety and efficacy determination by the FDA under our laws depends on knowing what those conditions are. For example, the dangers that might be encountered in taking Biltricide are much more than the dangers that you might have from a tranquilizer or some other drug and that is part of evaluating the benefit-risk ratio. You need to know what the conditions are. And it was all provided and agreed on.

The **Chairman**. Are you saying that the drug company should be the one that tells FDA what all those conditions should be?

Dr. **Wolfe**. Well, the drug companies, when they are trying to get any drug approved anywhere, whether it is in the United States or the Western European countries, do have to give that information. Any country that has a drug regulatory system needs to know the benefits versus the risk. The benefits are treating a serious life-threatening disease such as schistosomiasis so the answer is yes, it is part of any new drug application or comparable application in other countries.

The **Chairman**. Well, Health Action International in February of this year submitted testimony to a committee of the European Parliament on the issue of the export of pharmaceuticals from the European Economic Community. HAI called not for an absolute ban on the export of unapproved pharmaceuticals, but a disclosure, an information exchange system, and for the export of drugs severely restricted, withdrawn or even banned in the country of origin if the importing countries specifically requested it.

Now, this does not seem consistent with the blanket opposition to S. 2878 that has been their traditional position. Indeed, I do not think it is consistent with the position taken in the telegram HAI sent you for inclusion in your testimony.

It seems their message varies according to whichever audience they are in front of. Now, do you support the HAI proposal to the European Community or for the European Parliament?

Dr. **Wolfe**. Well, first of all, I think they are consistent because with respect to the European countries, which now have absolutely unlimited export ability on unapproved drugs, that would be an improvement over what is existing there. With respect to the United States, any loosening of our export prohibition would be a worsening. So I think that their two positions are perfectly consistent with one another. They are trying to make the European export situation better than it is, and they do not want our export situation, which is now optimal, to be worse than it is.

The **CHAIRMAN**. Well, is it your position that even given appropriate information from the World Health Organization, the Food and Drug Administration, and other national regulatory agencies, the individual developing countries are not capable of selecting the drug products appropriate for their own populations?

Is that really your position?

Dr. **WOLFE**. I am not sure I followed what your question——

The **CHAIRMAN**. Well, you seem to be saying to me that even if appropriate information is given by competent organizations like the World Health Organization, the Food and Drug Administration, other national regulatory agencies, that these countries are so bereft of the ability to choose for themselves that literally they are not capable of selecting the drug products that are appropriate to their populations.

Dr. **WOLFE**. Well, yes, for a number of reasons that I think are included in testimony.

The **CHAIRMAN**. But you are making your judgment——

Dr. **WOLFE**. They are not capable. One reason is——

The **CHAIRMAN**. I think that is the most arrogant statement I have heard here in a long time. I do not mean to be jumping on you but, by gosh, we live in the real world.

Dr. **WOLFE**. Maybe you did not listen to Mr. Lucas' testimony.

Mr. Lucas pointed out in his testimony some reasons why that is the case. They do not have the resources to have the kinds of medical——

The **CHAIRMAN**. Well, if they are going to watch over all their rights and their privileges, and their rights to self-determination, to make their own decisions.

Ms. **DRABBLE**. Let me just interject here.

The **CHAIRMAN**. Well, I have got to admit I just came back from a trip, and I have to admit there are some terrible situations that exist in many countries.

Dr. **WOLFE**. That is right. And most of them are solved by having the money to provide them with essential drugs now approved in the United States.

You show me a country like that, and I will show you that virtually all the drugs that they need are approved here and we can find a place for them.

The **CHAIRMAN**. We have had adequate testimony here that they will never get any help in some of these——

Dr. **WOLFE**. Any financial help?

The **CHAIRMAN**. Unless the United States comes out——

Dr. **WOLFE**. They may not have any financial help but that is a different problem.

The **CHAIRMAN**. No, no. They will not get any drug help either unless we start approaching it——in some of these cases that have been given here, unless we start approaching it in an intelligent way and get some impetus in this country, not just to throw money into these problems, which I think may be important in some instances, and hopefully Senator Kennedy and I can do some good there. I am prepared to do that.

Dr. **Wolfe**. That is the main problem.

The **Chairman**. Well, it is not the main problem. I think you are oversimplifying it and you are choosing ideology above substance.

Dr. **Wolfe**. What the ideology is, I have just been in India. There is a crying need there for essential drugs, for drugs, virtually all of which are approved in this country. There is no money to buy them. That is the problem.

The **Chairman**. They are crying for drugs that are not approved.

Dr. **Wolfe**. That is the problem in Ethiopia. The list that was provided from Ethiopia, virtually every drug on the list was approved in the United States. The couple that were not were thought by the Centers for Disease Control to be second- or third-rate drugs. Then it is a different kind of problem.

And I think it is easy to confuse the two problems. When the Pharmaceutical Manufacturers Association testified at a congressional hearing after the trip that Senator Kennedy and others made to Ethiopia, they made it sound as though this bill would solve the medical or drug need problems of Ethiopia. And the list of drugs that were submitted to support that just do not support it. We submitted it to Senator Simpson, the refutation of that, because the drugs are all available here. We need money. There is not money for food in Ethiopia nor for drugs in Ethiopia. It is a different problem, it is one that you and I probably agree fully on.

The **Chairman**. That is right. Not all of those drugs are available and not all of our companies are going to manufacture them——

Dr. **Wolfe**. If there is money for them, if there is no market for them.

The **Chairman**. That is right. If they have to go offshore to manufacture them and set up companies offshore in order to get it done because there is not that need here. You know, the World Health Organization's model essential drug list contains at least nine drugs which, under present law, cannot be exported from this country because they are not approved by the Food and Drug Administration.

Now, do you really believe that there is a good reason for continuing to ban the export of drugs which the World Health Organization deems essential for developing nations? Do you really believe that?

Dr. **Wolfe**. Well, I think that some, if not all those drugs are made by companies which do not have any manufacturing facilities in this country. They are already being made—even if they were made by companies that have manufacturing facilities here and abroad, as the industry said this morning, the main impact would not be to bring back to American soil new manufacturing facilities but rather for drugs that we do not have anywhere yet.

The **Chairman**. Let us assume that some of them are not.

Dr. **Wolfe**. Are not what?

The **Chairman**. Are not manufactured and are not available for one reason or the other.

Are you saying that our companies, which are the world class best companies to manufacture those drugs cannot do it without total approval by the FDA and export them to the countries that need them so badly?

Dr. **Wolfe**. Excuse me. The American companies are already making those drugs which they are interested in in foreign countries. I mean that is already being done. One reason is that the U.S. dollar is driving the situation in that direction, a completely separate and independent issue again.

The **Chairman**. Well, I might say that these are not the only drugs useful or desirable for treating the full range of human illnesses in developing countries, these nine I have been referring to. They are just the ones WHO deems "essential" in taking care of the most pressing needs of the greatest number of people.

Now, it does not make sense to recognize one category and ignore the other. You know, you say that one unfortunate consequence of letting foreign countries have access to the full range of drugs and make their own decisions is that they will spend too much money on frills or useless products and not focus sufficiently on the essentials.

Now——

Dr. **Wolfe**. There is good evidence for that.

The **Chairman**. Well, there may be.

Now, are you implying that if we allow a certain number of responsible unapproved drugs to be exported from the United States, which can now be produced abroad, for sale in those countries that more money will be wasted than it is now, or are you implying that if reform of the U.S. drug laws is turned back, somehow less money will be wasted abroad?

Dr. **Wolfe**. Well, that is the corollary of your other question. I said we do not know the answer to that. It is possible that a given drug would have much wider sales around the world if it were made here than if the same drug were made only in West Germany or the United Kingdom. I do not think we know the answer.

I think that the only thing we do know is that from the standpoint of the pride of this country and the worthwhileness of the "Made in the U.S.A." label, it would put blood on it to make these drugs here instead of somewhere else.

The **Chairman**. Well, I have got so many questions for you. Let me just ask you one more.

It has been further estimated in a PMA study that the beta blocker—it is Timenol?

Dr. **Wolfe**. Timenol.

The **Chairman**. Timenol.

Dr. **Wolfe**. Timoptic is the ocular form.

The **Chairman**. Let me get into that.

I am disturbed that we keep hearing broad charges that even the regulatory agencies of other developed countries are not to be respected because of examples of drugs that they have approved and then had to remove from the market.

I note here with particularity that FDA itself occasionally has to do this as well.

Dr. **Wolfe**. Right.

The **Chairman**. So it is not limited to other countries.

Dr. **Wolfe**. No. But it is much more common. Again I mentioned in the testimony that since 1960, 17 drugs not approved here but approved in the United Kingdom had to be banned, whereas only 3 drugs approved here but not in the United Kingdom had to be banned.

So if you look at drugs approved either in this country or the United Kingdom, we have a much better record than the United Kingdom.

The **Chairman**. Is there a representative of PMA present?

OK. Let me just say this. Can you people respond for the record to any of the examples of drugs approved abroad but not here which public citizen here has referred to or which were contained in the Moulton testimony? Would you be willing to provide that?

Voice. We have a copy of Dr. Moulton's testimony.

The **Chairman**. Will you provide that for the committee?

It is on page 14. I will keep the record open because I am concerned about this. And according to information that I have received, many of the examples used in the past are unreliable or so old as to be irrelevant. And this may be something we should explore in written supplements to the record.

So I would like both of you to—keep the record open for both of you to respond to this. I would like you to respond to each other.

Dr. **Wolfe**. The 66 United Kingdom examples were all in the last 2 years, they are not from the past. The others were from congressional testimony in 1979. But the ones that I looked at from 1983, 1984 all in the United Kingdom, and they are all from various international drug journals and so forth.

The **Chairman**. Well, in any event, you cite 38 deaths supposedly attributable to the use——

Dr. **Wolfe**. Right.

The **Chairman** [continuing]. Of Osmosin, for example, and conclude that this is evidence of inadequate regulatory action.

But the thing——

Dr. **Wolfe**. It is evidence of a double standard. That is what it is evidence of.

The **Chairman**. All right.

But the thing I never hear you mention is the cost in lives and suffering caused not by a too hasty approval but by delays in approval. You know, a good example is, as I was going to go into earlier, our experience with beta blockers, one of the most important class of drugs in this century for the treatment of hypertension and heart disease.

Now, what is it, propranolol?

Dr. **Wolfe**. Propranolol, right.

The **Chairman**. OK.

Propranolol, the first such drug to come into wide clinical use was introduced in the United Kingdom, as I understand it, in 1965 for cardiac arrythmia?

Dr. **Wolfe**. Yes.

The **Chairman**. I am not as sure as you are of pronouncing these things.

But in 1966 for treatment of angina, in 1969 for hypertension. The corresponding dates for the United States were 1968 and 1973 and 1976 respectively.

Now, it seems to me the cost in human lives in the United States alone can be counted in the tens of thousands because of the delay in approving beta blockers. And it has been estimated that the death rate from coronary heart disease has dropped by 27 percent between 1968 and 1972, and beta blockers are considered a major factor in this decline. And it has been further estimated, as I understand it, by the FDA or, excuse me, I think it is a PMA study——

Dr. **Wolfe**. Right.

The **Chairman** [continuing]. That the beta blockers, and I have mentioned it before, Timolol, is that it, Timolol is potentially able to prevent death in 10,000 patients per year who would not normally survive a second myocardial infarction.

Now, it was only in 1982 that the first beta blocker was approved in the United States for the reduction of death following a myocardial infarction. So, I just point out that I for one do not have any problem in saying that a number of foreign regulatory agencies are independently adequate and compare favorably with our own FDA. And I see no reason to disparage these agencies because they tend to approve certain drugs more quickly than FDA or experience a few more withdrawals.

Dr. **Wolfe**. Could I just respond——

The **Chairman**. Sure.

Dr. **Wolfe** [continuing]. Because that issue—the issue of the beta blockers——

The **Chairman**. Let me just continue my sentence and I will give you an opportunity to respond.

Dr. **Wolfe**. Fine.

The **Chairman**. Considering that sometimes enormous costs of the extra couple of years in the FDA pipeline, you know, I personally cannot conclude that the agencies are acting more recklessly or in contempt of their citizens' best interests. And I would point out that one reason that the FDA has become in some ways too willing to put off approval or reject an application until every last theoretical question has been laid to rest is the one-sided attention in the media received every time subsequent problems are discovered in drugs which are approved and marketed. And it does seem to me that the American people would be better served by a balanced attention revealing the cost of not being able to make use of medicines already approved elsewhere. There has got to be some better solution of these problems.

You know, I have to say this, I appreciate, you know, in some ways what you are trying to do but, in other ways, it seems to me that you are back in the 18th century, you are unwilling to admit that people have minds today and think for themselves in these Third World countries, that we have to be the granddaddy of the whole world and make all their decisions for them; that they just cannot make them like we can; that our FDA is the paramount organization in the world and nobody can compare with it. And does the fact that we have occasional problems throughout the rest of the world justify really not doing anything in this particular drug export area.

You know, jobs aside, and I think there is a good argument for jobs on drug export. I think even you would admit that. But jobs aside, that is not as important as the health of people. And I agree with you on that.

But the question is, you know, right now all the things that you criticize are going on, some of which would be alleviated by this particular bill and still give us the jobs to boot. It seems to me almost irreconciable for a consumer organization.

Well, one time you represent yourselves as a consumer organization. I know you intend to be. I know you are sincere in that. I have inestimable respect for your genius and intelligence. I am not just kidding about it. You are a very bright guy.

Dr. **Wolfe**. You are also.

The **Chairman**. And I just have to say I have respect for that.

Dr. **Wolfe**. Let me just respond to three things you said.

The beta blocker issue is one which I think you are misinformed about. There was a Wall Street Journal editorial several years ago saying that (*a*) 10,000 people a year were dying because of the unavailability of beta blockers, and (*b*) that the FDA should be therefore abolished.

You are a strong supporter of the FDA so I do not think you would agree with the second point.

The first point is incorrect, because once propranolol came on the market in the United States, it was being used as much here as anywhere else for preventing heart attacks. The FDA totally rebutted that statement of 10,000 deaths being prevented by another beta blocker being suddenly available. Timelol, which you correctly pointed——

The **Chairman**. Once it came on the market, the delay——

Dr. **Wolfe**. No, no. It was on the market less than a year after.

The **Chairman**. OK. So that is 8,000 people——

Dr. **Wolfe**. No, no. Excuse me. At that time it was not being used to prevent heart attacks. The use for preventing heart attacks is very recent. It is in the last several years. It is more than a decade after it came on the market.

When it came on the market, as you outlined, the main use was for treating arrythmias and so forth. And only later was it used for preventing heart attacks. So that there was really no lag in that.

And there is no evidence that Timolol is any better than propranolol.

The **Chairman**. Once that comes on the market, and it was used for arrythmia, doctors are not restricted in how they use that particular drug. So let us say it is only 1,000 deaths that could have been prevented.

Dr. **Wolfe**. There is no evidence that any deaths could be prevented, none, no evidence for that. The FDA has completely rebutted that.

Another statement which I think, you know, I think someone has given you information that is not correct is that during the——

The **Chairman**. If we never put that drug on the market, nobody would have died. So there is no reason——

Dr. **Wolfe**. Excuse me. Excuse me.

The **Chairman**. By your logic, if we had never put the drug on the market, nobody would have died.

Dr. **Wolfe**. No, no. The drug was on the market. No one was using it for that indication then. When it started——

The **Chairman**. That is your statement.

Dr. **Wolfe**. Pardon?

The **Chairman**. That is your statement.

Dr. **Wolfe**. Well, that is the FDA's statement. I mean, you do not think the FDA—the FDA has rebutted that whole argument.

The other point which I am making is that during the congressional Scheuer-Gore hearings——

The **Chairman**. Go ahead.

Dr. **Wolfe**. During the Scheuer-Gore hearings, a task force, including drug industry people, FDA people and so forth, were not able to cite one example of an important drug that was not available in the United States as a result of the drug lag. So I think that—and they obviously were aware of the beta blocker issue and so forth.

The **Chairman**. Will PMA cover that issue?

Dr. **Wolfe**. Well, PMA is the drug industry. It is not the FDA. I mean PMA is expected——

The **Chairman**. I think they have a desire to tell the truth just like you do. You both seem to be telling untruths from time to time. If both have to be blamed——

Dr. **Wolfe**. I think that the PMA often does tell the truth but they also are interested in selling drugs. In fact, I do not even think that they tell the truth by accident. I think it is on purpose a lot of the time.

The **Chairman**. Do you realize that by just watching their faces back there, I believe PMA is going to demand a copy of this record and they are going to frame that statement by you. [Laughter.]

Dr. **Wolfe**. For many, for some of the——

The **Chairman**. That is the only time you have ever been willing to admit that——

Dr. **Wolfe**. No, it is not. Joe Stetler will tell you I have done that before.

The **Chairman**. OK. Is that right, Joe?

Mr. **Stetler**. Even though that is right, I have a hard time shaking my head yes. [Laughter.]

Dr. **Wolfe**. That should be framed also. [Laughter.]

The views that I have expressed this morning are not simply my own views. As you will see when you read, as I am sure you will, the letters that we have received from all over the world, physicians in country after country, consumers from country after country, they do not believe that this law should be passed. It is not just me. I mean this law does not really have very much of an impact on the health of people in this country because it allows sales to the people outside the country. And the people in those countries are strongly opposed to it.

In addition to, you know, the statements which I read from the——

The **Chairman**. You know, it used to be that the argument was that the conservatives of this world are against everything. Really, you have usurped their position in so many ways.

Dr. **Wolfe**. No, I think that——

The **Chairman**. No. Wait a minute.

I really believe that genius that you have ought to be applied not so much politically, which I find the Nader organizations to be very effective at, much more effective politically than I think meritoriously, but let me just say this to you. I think you ought to apply that genius in some of these efforts to really helping some of these consumers in these Third World countries, and help us to write a better bill without saying knock out all antibiotics, make them come under the ban as well, do this, do that.

I really think you ought to help us.

Dr. **Wolfe**. Well——

The **Chairman**. And frankly I issue that challenge to you because as much as you and I disagree, you know, I like you personally a great deal, and you really are one of the most articulate spokesmen that I have had before the committee. And I know that you believe what you are saying, and that is the bottom line for me.

If I did not think you believed this—if I did not think you believed this, I would not have been so absolutely kind to you today as I have been. [Laughter.]

I mean I would have really been a lot tougher than I have been. I know you believe it. But, I think we make some good points too. I mean I have really tried to resolve these problems. I really am trying to do it. I am not trying to go out there and just pass a major piece of legislation just so Orrin Hatch can have another one added to the bills I have already passed. That is not my purpose. I do not think it is Senator Kennedy's purpose. We both have respect for you. And I would like to see you work with us.

Now, maybe I have got to move a little but I do not know. I think I have moved a lot to try and resolve some of the conflicts and problems that you are concerned about. I would like to see you move a little bit too. And I would like to see you work with us.

Dr. **Wolfe**. Let me tell you one issue that I would be glad to work on with you, and it is one that received a lot of attention this morning. It is the issue of the so-called tropical disease drugs.

I think—the issue of whether or not a company has ever asked the FDA for approval is an important one, that is, are there other tropical disease drugs that could easily be approved in the United States and thereby exported that, for reasons that we do not even understand, the company has never applied for approval. They think that it is going to take 10 years or something like that, which some drugs have taken, but it is mainly the unimportant drugs which take that long.

The **Chairman**. I think the company does not think it is economical to them at this particular point unless it is part of an overall drug market which justifies building plants to do more than just——

Dr. **Wolfe**. I think that we ought to look to see if there are more examples like Biltricide where we could do something right now to get approved through the Food and Drug Administration as safe and effective and therefore export now, not, you know, in a year or 10 or never as may happen if this bill does not pass.

I would be glad to work with you on that issue.

The **Chairman**. All right.

Dr. **Wolfe**. Because I think that something can be done under existing legislation and regulations with the model that you have heard about this morning.

The **Chairman.** I think I am going to have to be more tolerant too. I am going to have to—you know, I was raised a liberal Democrat. I know you feel that I strayed from the true path when——

Dr. **Wolfe.** I was raised as a conservative and I still am.

The **Chairman.** Now, let me just say this. I do not mean to demean you because I said I respect you and I said I have regard for you, I said I like you. Some of my friends do not like you at all. [Laughter.]

Dr. **Wolfe.** So maybe you should change your friends then.

The **Chairman.** Well, that may be. I am going to try and help them to change their views.

Dr. **Wolfe.** Very good. I will be glad to work with you on that. [Laughter.]

The **Chairman.** Let me just say this. I am going to end this session with this statement.

It seems to me that the bottom line on drug export is this. In my opinion, it will not make things worse for foreign consumers and may improve somewhat the quality of drugs they are now using. And it definitely will improve our economic condition. And, you know, the combination of these two factors provide for me a compelling argument in favor of a change in the law.

Now, I will try to keep an open mind on what you are saying and I will read these letters.

Dr. **Wolfe.** All right.

The **Chairman.** And I throw the door open to you let us see where we can agree and can go forward. I would like you to reassess and see if there is some way you could support a bill. On the other hand, I do not hold out much prospect of that with your testimony the way it is. But I would like to see us do more together.

And let me just say that even though I have disagreed with your testimony today in large measure, I have enjoyed this as much as any interchange I have had on the committee. And let me say with that we will keep the record open until this Friday. I would like to have PMA's or anybody else's response to this, what was testified today. And you can certainly—if you will provide a copy to these folks as well, then we would be happy to have your response to what they say. And we'll keep the record open for both of you.

It is a lively debate and a worthwhile one. And my goal here is to do what is best under the circumstances and what we should do.

And I will also challenge you to help us, as Senator Kennedy and I and others, I think, really good members of this committee try to do something to help with immunization processes around the world and other problems that really need to be addressed, and perhaps completely implemented by this country. This is something that I have had difficulty arriving at but which I am arriving at in more terms than less.

So let me just say that and recess this committee until further notice.

The **Chairman.** Thank you so much.

[Additional material supplied for the record follows:]

PublicCitizen

Congress Watch • Critical Mass Energy Project • Health Research Group • Litigation Group • Tax Reform Group

July 29, 1985

Honorable Orrin G. Hatch
Chairman
Committee on Labor and Human Resources
United States Senate
Washington, DC 20510

Dear Chairman Hatch,

The following are answers to questions submitted to Public Citizen by Senators Grassley (questions 1-4) and Metzenbaum (questions 5-9) of the Committee on Labor and Human Resources:

1. Mr. Mossinghoff made the point in his statement that the issue is really not what products will be sold abroad, but rather where they will be manufactured. Can you comment?

Isn't the issue really whether the drugs are safe or not? And if the drugs are safe, it seems unlikely that the "Made in the USA" label will be tarnished.

The U.S. pharmaceutical industry has argued vociferously that the issue at hand is not what products will be sold abroad, but where they will be manufactured. Current export policy, the drug firms claim, prevents the U.S. manufacture of drugs geared to Third World diseases and drains jobs from this country.

The real issues are how safe the drugs are and how much will be sold. The PMA has already estimated additional exports of between $400 million and $500 million in the first five years after permission to export unapproved drugs. Therefore, it is likely that lifting the export ban will serve to greatly increase the worldwide distribution of hazardous, ineffective, inappropriate, and expensive drugs.

The WHO has recommended a basic drug list of 200 items sufficient to serve the requirements of most Third World countries. Yet, Mexico has 80,000 products on the market, Brazil 30,000, Thailand 20,000, and India 15,000. We believe that the drug export proposal would only serve to worsen the situation of worldwide drug consumption and increase the risk of drug toxicity.

In testimony before your committee, FDA Commissioner Frank Young cited nine drugs on the WHO list of essential drugs that are not approved in the U.S. He stated that lifting the export ban would allow such vitally important medicines to be manufactured in our country. Of the nine drugs, only one (dehydroemetine) is manufactured by an American-based company (Merck, Sharp & Dohme). According to the *Handbook of Antimicrobial Therapy*, published by the highly respected *Medical Letter*, dehydroemetine is not a drug of choice for amebiasis. Therefore, current drug law does *not* keep essential drugs from the Third World. Any shortage of drugs in developing nations is due more to a lack of funds to pay for drugs and a dearth of resources devoted to piloting and producing new cures for tropical diseases than to restrictions in U.S. drug exports.

As for the drug industry's promise of more American jobs with the repeal of the export ban, most of the new U.S. production operations established to manufacture unapproved drugs would undoubtedly be located in Puerto Rico, where U.S. firms could take advantage of tax holidays, low-interest financing, and low-cost labor. Puerto Rico would effectively create an even greater magnet to lure U.S. drug industry capital *and* jobs away from the U.S. mainland.

Thus, the issue is not that the export ban keeps useful medicines from nations that need them. And the issue is not American jobs. The issue is whether the U.S. will condone risking the health and safety of international consumers so that U.S. drug companies can make profits on unapproved products.

The export of unapproved drugs necessarily entails the circumvention of the normal FDA process of testing and examining drugs. We believe that U.S. sales to foreigners of drugs not considered safe and effective for Americans would jeopardize the status of the "Made in USA" label--a label which is currently associated throughout the world with the highest standards of quality and safety.

2. Do you agree with the proposition that other countries in Europe, and Japan, have drug regulation agencies with comparable records to ours of protecting their citizens, as the manufacturers assert?

Do you agree with the proposition that approval by such a system would establish that a drug is safe and effective?

There are numerous examples showing that other industrialized nations' drug approval systems provide less protection than ours. In the past two years alone, six drugs that had recently been approved and were sold in the U.K. and other

Western European countries, but not in the U.S., were banned from the market for safety reasons.

If the proposed drug export bill were to become law, approval in a country with an "adequate" review authority is all that would be needed to trigger U.S. export approval to that country. However, the proposal before your committee provides no definition of an "adequate" drug approval system, and fails to require that those drug approval systems be equal to ours.

We believe that the U.S. has the best drug approval system in the world. Anything less than a standard of safety and effectiveness equal to that specified in section 505 of the Food, Drug and Cosmetic Act would not provide the protection that international consumers deserve.

3. Concern has been expressed here today about public health disasters which might occur were we to allow other countries' approval systems to govern sales abroad of American-made drug products.

What does the record show on this issue? Have we indeed had public health disasters as a consequence of distribution and use of American-made drugs manufactured abroad?

Yes, there have been public health disasters as a result of distribution and use of American-made drugs manufactured abroad. Osmosin, a slow-release arthritis drug, was approved in the U.K., West Germany, the Netherlands, Sweden, Switzerland, and other countries which are thought to have "adequate" drug regulatory systems. Osmosin was manufactured and widely marketed overseas by an American-based company, Merck, Sharp & Dohme. In September 1983, Osmosin was banned worldwide after causing 38 deaths and over 400 adverse reactions.

Within the past two years, five other drugs that were permitted abroad, but not in the U.S., were banned from the foreign market for safety reasons. Had the drug export law been in effect, these drugs would have been exportable from this country; had these drugs been made by U.S. companies in U.S. manufacturing facilities, America would have been responsible for foreign injuries and deaths.

Experience with antibiotics--already excluded from the export ban--has not been encouraging. Dr. Philip Lee, in his many books and in testimony before this committee, has identified major problems associated with the labeling, marketing, and use of antibiotics exported to Third World countries. His research has uncovered numerous instances in which U.S. drug firms minimized the drugs' hazards, exaggerated potential benefits, failed to provide specific information about appropriate uses, and heavily promoted drugs for inappropriate uses.

According to Dr. Lee, these unethical practices have already resulted in the emergence of at least six species of resistant strains of bacteria. Thus, the potential for an epidemic exists.

Public Citizen believes that permitting the U.S. export of unapproved drugs is a retrograde step for global health. The U.S. distribution abroad of drugs not deemed safe and effective by the FDA could result in numerous public health disasters.

4. Another point was made by the Commissioner of FDA, to the effect that each sovereign government has the responsibility for determining the types of drugs that can be imported. Do you agree with this assertion?

Many proponents of the drug export proposal claim that opposition to lifting the export ban is paternalistic, and that the U.S. should let other countries decide what is best for their own citizens.

Even if we assume that all of the countries on the list of nations with "adequate" drug approval systems have the ability to make reliable decisions about which drugs they will import, there is no requirement that health officials in these countries receive the kind of information which must be submitted to the FDA to support an application for U.S. approval. We believe that U.S. drug companies should be subject to American standards, and that the U.S. should not participate in the foreign sale of products which it will not allow to be sold in our own country.

Furthermore, as will be discussed in the next section, once a drug is manufactured in the U.S. and exported, it woud be extremely difficult to prevent reexports to other destinations. Many developing countries lack the funds, expertise, and government structures needed to protect their citizens from hazardous, ineffective, inappropriate, and expensive drugs. Should unapproved drugs be exported or secondarily exported to Third World nations, the results could prove disastrous.

5. In the course of the hearing, both the FDA Commissioner and the FDA General Counsel made the point that it would be extremely difficult to prevent the reexport or transshipment of drugs from countries on the approved list to countries not on the approved list--most notably those in the Third World. Do you agree or disagree? Why?

The Genentech drug export proposal disallows direct shipment of unapproved drugs to Third World countries, but it fails to ban secondary export to developing nations. Under this proposal, Western Europe could become a mere way station for drugs en route to developing nations, especially since Western European countries do not themselves restrict exports. The effective result would likely be an uncontrolled flow of unapproved drugs into the Third World.

Public Citizen agrees with FDA Commissioner Young and FDA General Counsel Scarlett that there would be no way of policing reexports of pharmaceuticals. In addition to the FDA's views on this matter, several U.S. drug company officials have also admitted, privately, that there is no practical way to prevent reexport to the Third World once an unapproved drug is shipped from the U.S. to a country with an "adequate" drug approval system. Two WHO officials also stated that they saw no way such reexport could be prevented.

Thus, any legislation which would "limit" drug exports to countries with "adequate" drug approval systems is de facto support for eventual shipment, via reexport, of these unapproved drugs to Third World countries. Such legislation would facilitate the process of health destruction in developing nations, thereby serving to contravene the distinct purpose of WHO.

6. I believe your organization has studied the Genentech proposal in some detail. Do you view the proposal as a compromise which will provide additional protection for foreign consumers?

Unlike S.2878, a drug export bill introduced in the 98th Congress, the Genentech proposal would limit the export of unapproved drugs to industrialized nations. Public Citizen does not view this feature as a compromise which would provide additional protection for foreign consumers. Despite its cosmetic appearance, the Genentech proposal would have the practical effect of facilitating the sale of unapproved drugs to the Third World. As discussed in the previous section, under the Genentech scheme, an importing country would simply become a middleman for reshipment of unapproved drugs to the Third World.

7. We have heard that the reason the drug industry needs this bill is to prevent the export of valuable technology to West Germany and Japan. What is your view of this argument?

The drug industry--and particularly some biotechnology firms--argue that requiring foreign manufacture of unapproved drugs results in the transfer of technology from the U.S. to foreign countries. As you can see from the enclosed article, limits on drug exports have little to do with this Rockville, Maryland firm's motivations for sharing technology with a foreign firm or building a plant on foreign soil. "It's not cost-competitive to produce here for [the East Asian] market," says Thomas Li, president of Biotech Research labs. He cited tax advantages and lower shipping and labor costs as some of the reasons for forming the joint venture and for manufacturing the products overseas rather than in the U.S.

Companies do not usually transfer technology or enter into foreign ventures primarily to compensate for restrictions on drug exports. The main reasons why firms engage in joint ventures are to:

- gain foreign capital to finance research;
- gain engineering personnel and production facilities not available or affordable in the U.S.;
- gain access to markets U.S. companies could not otherwise move into because of the desire of foreign countries to develop their own exports;
- gain scientific knowledge that they would otherwise not get.

8. How do you respond to the argument that drug companies can produce these products overseas despite the U.S. ban, so our ban, in effect, provides no practical protection to foreign consumers?

The drug industry has argued that drugs not approved for sale in America will continue to be supplied to international consumers by foreign competitors and American companies with foreign production facilities. However, the failure of other countries to control their drug exports responsibly is hardly justification for the U.S. to intentionally decide to do the same.

Obviously, the U.S. has no direct power to control activities which take place outside its own borders. But we can decide what actions are permitted in our own country. In order to ensure that American-based companies are not responsible for exporting risks and hazards to foreign consumers, we must insist that companies producing drugs in our country remain subject to American laws and standards.

9. What further changes do you believe are necessary in these proposals to protect consumers in the context of drug exports?

Public Citizen would not support any proposal which would allow the export of unapproved drugs to foreign countries. Regardless of the profits and jobs which will be created by lifting the export ban, the lives and health of international consumers must not be jeopardized in order to subsidize the economic interests of the drug and biotechnology industries.

If Congress does anything to amend current law, it should:

- prohibit the presently allowed export of unapproved antibiotics;
- require that every drug approved in the U.S. that is sold and distributed in another country contain the American labelling (translated into the appropriate language).

At your request, we are enclosing Public Citizen's December 21, 1984, letter to Dr. Halfdan Mahler, and the January 16, 1985, response from Dr. J. Cohen.

Please don't hesitate to contact us if you need additional information.

Respectfully submitted,

Sidney M. Wolfe, M.D.
Director

Pauline Sobel

Pauline Sobel
Researcher

Enclosures

Public Citizen

Congress Watch • Critical Mass Energy Project • Health Research Group • Litigation Group • Tax Reform Group

July 22, 1985

Honorable Orrin G. Hatch
Chairman
Committee on Labor and Human Resources
United States Senate
Washington, D.C. 20510

Dear Chairman Hatch,

The following is a response to the PMA's analysis of Public Citizen's June 5, 1985, testimony before the Senate Committee on Labor and Human Resources concerning U.S. export of unapproved drugs:

One of the numerous objectionable features of the proposed legislation to lift the export ban is the reliance on actions of foreign countries with "adequate" drug approval systems to trigger U.S. exports of unapproved drugs.

Neither S. 2878 nor the Genentech proposal contain the requirement that an importing foreign country rely on a standard of safety and effectiveness comparable to that specified in section 505 of the Food, Drug and Cosmetic Act.

To show that other industrialized nations' drug approval systems provide less protection than ours, we cited 19 examples of toxic drugs that have been permitted abroad, but not in the U.S. Thirteen of these 19 examples were originally offered by Dr. Barbara Moulton, a former FDA medical officer, in her 1979 congressional testimony.

As the PMA correctly noted, Chlormadinone was indeed sold in the U.S., and Ethynerone, Cinanserin, and Triflocin were never sold in any country at any time. However, most of the 13 drugs Dr. Moulton mentioned are excellent examples of drugs approved by "sophisticated" countries other than the U.S. that were marketed abroad with disastrous results. Most notably among them were:

*__Thalidomide__ -- a hypnotic/sedative responsible for causing thousands of still-births and tragically-deformed children across Europe.

*__Isoproternol__ Inhalers -- a highly concentrated form of this drug given to primarily teenaged asthmatic patients is thought to have caused 3,500 deaths in England and Wales.

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***Aminorex**-- an appetite suppressant linked to hundreds of cases of primary pulmonary hypertension, including 26 deaths in Switzerland. The PMA has commented that Aminorex was never approved in either the U.K. or the U.S. However, it is still a perfectly valid example. Dr. Moulton was discussing drugs permitted anywhere abroad, but not in this country, and was not referring specifically to the U.K. Aminorex was marketed in Switzerland in the mid-1960s. Switzerland has been targeted as a country with an "adequate" drug approval process.

***Stalinon** -- a treatment for boils that has been linked with at least 110 deaths in France.

***Practolol** -- a beta-blocker that was banned in the U.K. in 1976 for safety reasons. This drug was used in the Bakke study-- a study whose methodology and findings the PMA supports.

***Pronethalol** -- another beta-blocker that was banned in the U.K. in 1965 for safety reasons. This drug was used in both the Bakke and FDA studies -- studies whose methodologies and findings the PMA supports.

The additional six examples of toxic prescription drugs offered in our testimony were all sold in the U.K. and other Western European countries, but not in the U.S. All six were banned from the market within the past two years for safety reasons.

One of the most dangerous and widely marketed of the six was Osmosin, a slow-release arthritis drug that was found to cause intestinal perforation and was linked to 38 deaths and 400 serious adverse reactions. Comments in the PMA submission regarding Osmosin would lead one to believe that the toxic form of this drug is still sold in the U.S. today. The sustained-release dosage form of Osmosin that was banned worldwide in September 1983 is obviously not the same dosage form of indomethacin that is still available in the U.S. and elsewhere.

The other five recently banned drugs were Zelmid, an antidepressant linked to Guillain-Barré syndrome and paralysis; Flosint, an arthritis medication suspected of causing gastrointestinal reactions and an unknown number of deaths; Methrazone, another arthritis drug with a poor overall adverse reaction profile; Althesin, an anesthetic found to cause anaphylactic shock; and Flenac, an arthritis drug that was recalled after causing over 15,000 adverse reactions and an unstated number of deaths.

The PMA asserts that these last five drugs were discovered and developed by foreign-based companies in foreign countries, so removal of the U.S. export ban would not have had any impact on their development and distribution abroad. Furthermore, two of these drugs (Methrazone and Althesin) were never submitted to the FDA for marketing approval, and two (Flosint and Flenac) were submitted to, but not approved by, the FDA.

The point is that any drug sold in a country with a "competent" review authority, but not approved in the U.S., would become exportable if the proposed export bill were to become law. Approval in a country with an "adequate" drug regulatory system is all that would be needed to trigger U.S. export approval to that country. Furthermore, the proposed legislation to lift the export ban would authorize a U.S. company to export an unapproved drug even if the company failed to submit a New Drug Application, let the NDA lapse, or failed to win FDA approval with a submitted NDA.

Had any of these six recently banned drugs been manufactured in the U.S. -- as the proposed drug export bill would have permitted -- U.S. drug firms would have been responsible for the deaths and injuries of foreign consumers.

As stated in our testimony, although the authors of two recently published studies concluded that drug safety withdrawals are similar in the U.S. and the U.K., we believe that there are problems with their analyses. In both studies, the outcome is distorted because this recent alarming streak of six U.K. bans is omitted. In addition, the methodology used to choose drugs to be considered in the Bakke study is questionable. The reason for excluding the recently withdrawn antiemetic preparation Bendectin/Debendox, for example, makes no sense whatsoever. Furthermore, in the final analyses of both studies, drugs approved and banned in both countries are treated equally, without distinguishing which country sold the drug for a longer time period.

We believe that the U.S. has the best drug approval system in the world. If a drug has not been found by the FDA to be safe and effective, it should not be domestically manufactured and exported to international consumers.

If the drug industry believes that the stringent standards set forth in the Food, Drug and Cosmetic Act cause untoward delays in the approval and marketing of important new drugs, it should strive to revise, rather than circumvent, the regulations.

Respectfully submitted,

Sidney M. Wolfe, M.D.
Director

Pauline Sobel

Pauline Sobel
Researcher

WRITTEN TESTIMONY OF

DR. RONALD E. CAPE
CHAIRMAN AND CHIEF EXECUTIVE OFFICER
CETUS CORPORATION,

PRESIDENT, INDUSTRIAL BIOTECHNOLOGY ASSOCIATION

BEFORE THE
SENATE COMMITTEE ON LABOR AND HUMAN RESOURCES
IN SUPPORT OF
AN AMENDMENT TO THE FEDERAL FOOD, DRUG
AND COSMETIC ACT
PERMITTING EXPORT OF NEW DRUGS
PRIOR TO FDA APPROVAL

JUNE 5, 1985

WRITTEN TESTIMONY OF DR. RONALD E. CAPE

Mr. Chairman, and members of the committee, thank you for the opportunity to present this testimony. I am Ronald E. Cape, and I am Chairman and Chief Executive Officer of Cetus Corporation, a biotechnology company that I co-founded in 1971 and that is now engaged primarily in the development of a new generation of pharmaceutical products. I am also President of the Industrial Biotechnology Association, a trade organization comprised of companies actively involved in biotechnology that range in size from quite small, new enterprises to the largest corporation in the world.* In this testimony I hope to communicate to you my concern about the impact of present drug export restrictions on our biotechnology industry, and to express Cetus' wholehearted support for an amendment that would remove a serious threat to our future success.

Biotechnology in America

As background to the discussion of existing law and the proposed amendment, I would like first to describe both Cetus Corporation and the biotechnology industry in general. Since 1971, Cetus has pioneered the commercial application of biotechnology in the development of new or improved products for human and animal healthcare and for the production of food, energy and chemicals. In performing this work Cetus has advanced the application of the modern tools of recombinant DNA and monoclonal antibody research. Cetus-modified microorganisms are currently used in the commercial production of antibiotics, vitamin B_{12}, and an animal vaccine containing components developed by Cetus through recombinant DNA technology.

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*Membership list attached.

Cetus has produced two potential therapeutic products through recombinant DNA that are now in Phase II human clinical trials. Initial clinical data have indicated that these two products, beta-Interferon and Interleukin-2, may have significant value in the treatment of certain cancers and infectious diseases, including AIDS.

The power and promise of biotechnology is undisputed throughout the world -- it is expected to be a dominant force in world industry over the next quarter-century, much the same as information processing has had a revolutionary impact in our recent past. And, for the time being, the United States' leadership in this field is equally undisputed. The people of the United States stand to gain enormously from the projected applications of this new science, including means of diagnosing and treating diseases that are presently incurable, such as cancer or AIDS, microbial pesticides that can replace dangerous chemicals, food crops that require smaller amounts of artificial fertilizer and pesticides, cheaper and more efficient sources of energy, and means of cleaning up environmental disasters. Also of vital importance is the economic benefit, in terms of jobs, tax revenues, trade balances and capital investments, that will accrue to the nations that are most successful at fostering the development of this pioneering industry through the early stages of commercialization.

Cetus views the current restrictions on drug exports as a very serious threat to the United States' leadership in biotechnology and indeed to our continued success as a pioneering enterprise in this field. In order to understand why we are especially vulnerable, several key features of our business should be kept in mind:

- The United States is beginning to face a real threat to its first-place position as other nations have undertaken massive programs to catch up scientifically and rush products to the marketplace. Japan has declared biotechnology one of its highest national industrial priorities for the 1980s. Meanwhile, the United States' public commitment to basic biomedical research, which has had much to do with our present leadership position, has been eroding steadily. Congress is keenly aware of the threat of international competition in biotechnology. Last year the Office of Technology Assessment (OTA) published a report manifesting the urgent need for progressive legislation. Commercial Biotechnology: An International Analysis (Washington, D.C.: U.S. Congress, Office of Technology Assessment, OTA-BA-281, January 1984) ("OTA Report"). The report summarizes that:

> Although the United States is currently the world leader in both basic science and commercial development of new biotechnology, continuation of the initial preeminence of American companies in the commercialization of new biotechnology is not assured. Japan and other countries have identified new biotechnology as a promising area for economic growth and have therefore invested quite heavily in R&D in this field.
> (OTA Report, page 3.)

- Many of the most innovative biotechnology companies are smaller, independent companies without vast financial resources. Even though companies like Cetus have been fortunate enough to receive substantial financial support from investors, these funds can be exhausted very quickly in bringing new pharmaceutical products to market. A genetically engineered protein that may have cost a company $10 million in the research and development phase may cost more than $50 million over 5-8 years to complete the clinical trials necessary to obtain FDA approval. Assuming a modest-sized company has a range of targeted products, these high costs will keep it, at best, in a state of delicate financial equilibrium until it can begin earning sizable revenues on those products.

Moreover, continued support from investors will surely dry up if legal restrictions prevent the innovators from succeeding financially.

- Manufacturing facilities required for making biotechnology products require state-of-the-art technology and are extremely expensive. Cetus has built a process development facility in California, at a cost of tens of millions of dollars, that is designed to produce enough material to supply the projected worldwide demand for our genetically engineered products at least in the near term. Building such an ultra-high technology facility, and making it run properly, requires scientific expertise and practical know-how that only a handful of companies in the world (most of them in the United States) now have.

- Access to the export market is critical for biotechnology companies making pharmaceutical products. Western Europe and Japan together constitute one-half to two-thirds of the total worldwide market for many types of human therapeutic products, so that without access to these markets, United States biotechnology companies would lose in excess of 50% of available sales. We acknowledge as a fact of life that regulatory approval for drugs is usually obtained elsewhere before it is obtained in the United States. But if access to these early markets is delayed, foreign competitors will have the opportunity to establish an earlier market presence than we will, even if they are not the first to develop the product (and even if their product is inferior to an earlier-developed version), thereby putting the United States company at a disadvantage both abroad and in the domestic market.

The Impact of Existing Export Restrictions

Under existing law, an American manufacturer may not export drugs or biological products until the FDA has approved them for marketing within the United States, even if regulatory approval has already been obtained in the importing country. While it prohibits exports under these conditions, this law does not prevent a company with sufficient resources from producing drugs overseas. The purpose of this unusual provision is uncertain; there is strong evidence that it was completely unintentional.* But regardless of the intent, the effect of this restriction is to erect a major trade barrier against the small, pioneering biotechnology companies that have helped make the United States the leader in this field. It forces us to make choices between several undesirable alternatives:

1. If we had the funds, we could build additional expensive production facilities abroad, as major pharmaceutical firms have done in the past. By manufacturing overseas we could avoid the export restriction altogether. But this alternative is not a practical one. It is expensive enough to build one of our sophisticated biotechnology facilities in the United States; to build two is beyond the fiscal limits of the smaller and most innovative companies in the business. Some foreign nations, in order to attract technology and capital investment and perhaps in an attempt to recreate our unique American entrepreneurial climate, are now offering substantial incentives to companies willing to build biotechnology plants within their borders, and at least one United States-based company has already committed to build a facility in one of these countries as a means of hedging its bets against export restrictions. However, even with these "sweeteners," building an extra facility is not an attractive alternative under normal circumstances, and it is not in anyone's interests to be forced to make a decision to locate abroad.

*The export prohibition actually applies to unapproved "new drugs," and not to unapproved drugs that are not classified as "new". This different treatment apparently resulted from a drafting error when the concept of "new drug" was introduced in the 1938 amendment to the Food, Drug and Cosmetic Act.

While the expense of building overseas plants looms as an enormous barrier to smaller biotechnology companies like Cetus, it is an unnecessary and unreasonable burden to force upon even the large pharmaceutical corporations. Donald H. Rumsfeld, now Chairman of G.D. Searle & Co., recently complained of the "roaring idiocy" of export restrictions that forced his pharmaceutical company to locate a multimillion dollar manufacturing plant in England at the time of a $120 billion trade deficit in the United States. The plant will initially ship to Mexico and Europe, and eventually its products will be imported back into the United States!

2. We could wait until we receive FDA approval before selling our products abroad. Essentially this would be a prescription for failure. It would be totally against the interest of our shareholders, totally against anyone's interest. It would give foreign competitors several years of lead time in which they would probably catch up with us scientifically and dominate the market for a product before we could sell a single unit.

3. We could license our technology so that a foreign company could manufacture our products and sell them overseas. But, aside from yielding smaller revenues to us, this would require us to transfer not only information about the specific product, but also our manufacturing know-how, developed over years of painstaking, expensive research. Since this approach affords foreign drug importers the opportunity to catch up technologically in a single bound, they are quick to point out in negotiations that they want our technology because United States law would make us an unreliable supplier.

To illustrate what this type of technology transfer means, let me use as an example Interleukin-2 ("IL-2"), a product in which Cetus is a recognized world leader. IL-2 is a promising new genetically engineered drug for potential treatment of various forms of cancer, serious infectious diseases and AIDS. IL-2 is a protein that regulates the body's immune system. Cetus scientists have isolated this regulator, which appears in tiny quantities in the human body, and manipulated the genetic material that instructs the body's cells to produce the protein. Using its knowledge of the genetic code, Cetus then found ways to biochemically modify the gene for this protein and thereby, via cloning and expression, to manufacture large quantities of a pure, improved protein we call a "mutein"*. Someday this kind of achievement will become commonplace, but only a few years ago it was impossible, and today it is the object of admiration throughout the world. IL-2 made by Cetus is now being studied in 250 patients, and we have been encouraged by the types of responses already observed in cancer patients with Kaposi's Sarcoma (associated, as you know, with AIDS) chronic leukemia, ovarian carcinoma, colon carcinoma and melanoma.

We hope to be able to market IL-2 in the United States in 1988. But we also hope to introduce the drug in Western Europe and Japan as soon as appropriate foreign regulatory approval is obtained, and past experience tells us that, in all likelihood, this will happen before approval is obtained domestically. If we were to enter foreign markets by licensing the manufacture of IL-2 to a foreign company, we would probably have to teach that company not only how we make IL-2, but also how our "mutein" program works, how to build an appropriate biotechnology fermentation facility, and other associated know-how that they could use for making and purifying a whole range of new products. If we don't agree to transfer the technology in order to penetrate foreign markets, we are likely to be overtaken by foreign competitors who are now about two years behind us in developing IL-2 for clinical use. Most importantly, this is the prescription for the loss of the United States' golden opportunity to lead the world in this industry.

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*The uniqueness of this development is reflected in the recent award to Cetus of U.S. Patent No. 4,518,584, entitled "Human Recombinant Interleukin-2 Muteins". How ironic it will be if, notwithstanding this remarkable achievement, foreign interests obtain the major benefits of its commercialization!

In summary, this is a situation in which American biotechnology companies, and the United States itself, can only lose. The effect of this barrier is not only the injury it causes to innovative businesses like ours. It will also result in our sending abroad valuable technology, capital investment, and high-technology jobs--commodities the United States cannot afford to lose. In discussions about our drug export restrictions with leaders of the foreign pharmaceutical businesses, their reaction invariably is one of astonishment and amusement. At a time when the United States is fighting so hard to ease its trade deficit and to remove foreign protectionist barriers to American products, how can the Americans possibly justify keeping in effect a trade barrier against themselves? Indeed, how can we justify to ourselves a failure to correct an irrational obstruction that will give our competition an edge in yet another important industry? How long does it take us to learn this lesson?

Conclusion

Action is urgently required to ensure that the damage caused by current export restrictions to American biotechnology is kept to a minimum. Cetus supports prompt adoption of legislation such as Senate Bill 2878 introduced last year by Senator Hatch, or an alternative bill that would permit Cetus, without undue restriction or delay, to export drugs to its foreign trading partners when the importing nations have approved the drugs for sale.

I would like to emphasize in closing that this is not, fortunately, an area where Congress is required to balance the interests of opposing American constituencies. What is required simply is fixing a statutory provision that helps no one but that hurts and threatens to hurt many. In fact, since only the smaller companies are effectively proscribed from selling products abroad under the existing law, the harm falls most heavily on the innovative companies that have pioneered biotechnology applications in this country. In short, we must avoid shooting ourselves in the foot at the start of one of the most important races of this or any other century. A balanced amendment to the current export restrictions is an action by which we all stand to gain. It will help ease the increasing trade imbalance, it will help the United States maintain its lead in a promising, economically important new technology, and it will encourage companies to locate their plants in this country. Therefore we urge passage of such an amendment at the earliest possible time. We would be pleased to work with you and your staff on this important matter.

May 1985

IBA

MEMBER COMPANIES
INDUSTRIAL BIOTECHNOLOGY ASSOCIATION

AGRIGENETICS CORPORATION
Boulder, Colorado

ALLELIX INC.
Mississauga, Ontario
Canada

ALLIED CORPORATION
Morristown, New Jersey

AMGEN
Newbury Park, California

AMERICAN CYANAMID COMPANY
Wayne, New Jersey

AMICON CORPORATION
Danvers, Massachusetts

BIOGEN INC.
Cambridge, Massachusetts

BIOTECHNICA INTERNATIONAL, INC.
Cambridge, Massachusetts

BIOVEC TECHNOLOGY, INC.
Seattle, Washington

CALGENE, INC.
Davis, California

CALIFORNIA BIOTECHNOLOGY INC.
Mountain View, California

CENTOCOR
Malvern, Pennsylvania

CETUS CORPORATION
Emeryville, California

CIBA-GEIGY CORPORATION
Greensboro, North Carolina

COLLABORATIVE RESEARCH INC.
Lexington, Massachusetts

CPC INTERNATIONAL, INC.
Englewood Cliffs, New Jersey

DAMON BIOTECH, INC.
Needham Heights, Massachusetts

THE DOW CHEMICAL COMPANY
Midland, Michigan

EASTMAN KODAK COMPANY
Rochester, New York

E.I. du PONT de NEMOURS & COMPANY
Wilmington, Delaware

EXXON RESEARCH & ENGINEERING COMPANY
Linden, New Jersey

FMC CORPORATION
Princeton, New Jersey

GENENTECH, INC.
S. San Francisco, California

GENETICS INSTITUTE
Cambridge, Massachusetts

GENEX CORPORATION
Rockville, Maryland

GIST-BROCADES USA INC.
Charlotte, North Carolina

HOFFMANN-LA ROCHE INC.
Nutley, New Jersey

IMMUNEX CORPORATION
Seattle, Washington

JOHNSON & JOHNSON
New Brunswick, New Jersey

LIFECODES CORPORATION
Elmsford, New York

MELOY LABORATORIES, INC.
Revlon Health Care Group
Springfield, Virginia

MOLECULAR GENETICS, INC.
Minnetonka, Minnesota

MONSANTO COMPANY
St. Louis, Missouri

MYCOGEN CORPORATION
San Diego, California

PHARMACIA, INC.
Piscataway, New Jersey

PHILLIPS PETROLEUM COMPANY
Bartlesville, Oklahoma

**

ROHM AND HAAS COMPANY
Philadelphia, Pennsylvania

SANDOZ, INC.
East Hanover, New Jersey

SCHERING-PLOUGH CORPORATION
Madison, New Jersey

G.D. SEARLE & COMPANY
Chicago, Illinois

SHELL OIL COMPANY
Houston, Texas

SMITH KLINE & FRENCH LABORATORIES
Philadelphia, Pennsylvania

STANDARD OIL COMPANY (Indiana)
Naperville, Illinois

TRANSGENE
Paris
France

THE UPJOHN COMPANY
Kalamazoo, Michigan

** PIONEER HI-BRED INTERNATIONAL, INC.
Des Moines, Iowa

IFPMA CODE OF PHARMACEUTICAL MARKETING PRACTICES

CODE FIIM DE PRATIQUES DE COMMERCIALISATION DES PRODUITS PHARMACEUTIQUES

CODIGO FIIM DE NORMAS DE COMERCIALIZACION DE PRODUCTOS FARMACEUTICOS

INTERNATIONAL FEDERATION OF PHARMACEUTICAL
MANUFACTURERS ASSOCIATIONS (IFPMA)

FEDERATION INTERNATIONALE DE L'INDUSTRIE
DU MEDICAMENT (FIIM)

FEDERACION INTERNACIONAL DE LA INDUSTRIA DEL
MEDICAMENTO (FIIM)

The INTERNATIONAL FEDERATION OF PHARMACEUTICAL MANUFACTURERS ASSOCIATIONS (IFPMA) is a nongovernmental organization having as its members, direct or through regional organizations, the pharmaceutical industry associations of 47 countries in all parts of the world. The Federation was founded in 1968 and was admitted into official relations with the World Health Organization in 1971. It has since then obtained consultative status with the World Intellectual Property Organization, the United Nations Industrial Development Organization, the United Nations Conference on Trade and Development, the U.N. Economic and Social Council, the United Nations Children's Fund (UNICEF) and the Council of Europe.

The objects of the Federation are:

- *a. to assure permanent contact among its members;*
- *b. to deal with all questions of common interest, for example, in the fields of health legislation, science and research, in order to contribute to the advancement of the health and welfare of the peoples of the world;*
- *c. to promote and support continuous development throughout the pharmaceutical industry of ethical principles and practices voluntarily agreed on;*
- *d. to contribute expertise to, and to cooperate with, national and international organizations, governmental or nongovernmental, having the same aims; and*
- *e. to coordinate the efforts of its members towards the realization of the above objects.*

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IFPMA CODE OF PHARMACEUTICAL MARKETING PRACTICES

See also Supplementary Statement
(page 21 – English only)

Preamble

The Statute of the Federation article 3 states that one of the objects of the Federation is «to promote and support continuous development throughout the pharmaceutical industry of ethical principles and practices voluntarily agreed on» and «to coordinate the efforts of its members towards the realization of the above objects».

It is believed that in keeping with the pharmaceutical industry's international responsibilities, the members of the Federation will be prepared to accept certain obligations, insofar as their marketing practices are concerned, and to ensure respect for them.

IFPMA recommends a Code of Marketing Practices to its member associations, recognizing the difficulty of setting out a simple Code which will be applicable in all parts of the world. It seems clear that national and regional conditions and legal restrictions will continue to vary to such an extent as to make a simple world Code impractical. Nevertheless, the Federation believes that it has a duty to encourage its member associations to either introduce such Codes of Practices or where such Codes already exist, to continually re-examine and where necessary revise them so that a voluntary system based on such a Code keeps pace with modern medical knowledge and changing health services and conditions.

It is recognized that many individual member associations of IFPMA have laid down their own Codes of Marketing Practices and this recommended Code is not intended to replace similar Codes or instruments already in force by members of the Federation. The following voluntary Code is therefore put forward as a model for IFPMA's member associations.

A Code of Marketing Practices of this sort should be the responsibility of member associations who should also provide guidance to their members on matters of compliance and interpretation.

Obligations of Industry

The obligations of the industry may be identified as follows:

The pharmaceutical industry, conscious of its special position arising from its involvement in public health, and justifiably eager to fulfil its obligations in a free and fully responsible manner, undertakes:

- to ensure that all products it makes available for prescription purposes to the public are backed by the fullest technological service and have full regard to the needs of public health;
- to produce pharmaceutical products under adequate procedures and strict quality assurance;
- to base the claims for substances and formulations on valid scientific evidence, thus determining the therapeutic indications and conditions of use;
- to provide scientific information with objectivity and good taste, with scrupulous regard for truth, and with clear statements with respect to indications, contra-indications, tolerance and toxicity;
- to use complete candour in dealings with public health officials, health care professionals and the public.

Suggested Code of Marketing Practices

We hereby declare our intention to voluntarily conform to the following Code of Marketing Practices:

I. General Principles

1. The term "pharmaceutical product" in this concept means any pharmaceutical or biological product intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in humans, or to affect the structure or any function of the human body, which is promoted and advertised to the medical profession rather than directly to the lay public.
2. Information on pharmaceutical products should be accurate, fair and objective, and presented in such a way as to conform not only to legal requirements but also to ethical standards and to standards of good taste.
3. Information should be based on an up to date evaluation of all the available scientific evidence, and should reflect this evidence clearly.
4. No public communication shall be made with the intent of promoting a pharmaceutical product as safe and effective for any use before the required approval of the pharmaceutical product for marketing for such use is obtained. However, this provision is not intended to abridge the right of the scientific community and the public to be fully informed concerning scienti-

fic and medical progress. It is not intended to restrict a full and proper exchange of scientific information concerning a pharmaceutical product, including appropriate dissemination of investigational findings in scientific or lay communications media, nor to restrict public disclosure to stockholders and others concerning any pharmaceutical product as may be required or desirable under law, rule or regulation.

5. Statements in promotional communications should be based upon substantial scientific evidence or other responsible medical opinion. Claims should not be stronger than such evidence warrants. Every effort should be made to avoid ambiguity.
6. Particular care should be taken that essential information as to pharmaceutical products' safety, contraindications and side effects or toxic hazards is appropriately and consistently communicated subject to the legal, regulatory and medical practices of each nation. The word "safe" must not be used without qualification.
7. Promotional communications should have medical clearance, or where appropriate, clearance by the responsible pharmacist, before their release.

II. Medical Representatives

Medical representatives must be adequately trained and possess sufficient medical and technical knowledge to present information on their company's products in an accurate and responsible manner.

III. Symposia, Congresses and other Means of Verbal Communication

Symposia, congresses and the like are indispensable for the dissemination of knowledge and experience. Scientific objectives should be the principal focus in arranging such meetings, and entertainment and other hospitality shall not be inconsistent with such objectives.

IV. Printed Promotional Material

Scientific and technical information shall fully disclose the properties of the pharmaceutical product as approved in the country in question based on current scientific knowledge including:

- The active ingredients, using the approved names where such names exist.
- At least one approved indication for use together with the dosage and method of use.
- A succinct statement of the side-effects, precautions and contraindications.

Except for pharmaceutical products where use entails specific precautionary measures, reminders need not necessarily contain all the above information providing that a form of words is used which indicates clearly that further information is available on request.

Promotional material, such as mailings and medical journal advertisements, must not be designed to disguise their real nature and the frequency and volume of such mailings should not be offensive to the health care professionals.

V Samples

Samples may be supplied to the medical and allied professions to familiarize them with the products, to enable them to gain experience with the product in their practice, or upon request.

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Supplementary Statement

IFPMA and its Member Associations agreed the following statement in March 1982 which they believe will further demonstrate the industry's commitment to the observance and monitoring of the Code. It should be emphasized however that this supplementary statement does not vary in any way the provisions of the original Code.

1. Major pharmaceutical multinational companies (MNCs) belonging to IFPMA Member Associations, have been asked to commit themselves to the observance of the Code wherever they market their products.
2. To meet the criticism that many Third World countries are not aware of the indications, contra-indications, side effects etc. of individual drugs that have been accepted in the developed countries, IFPMA will offer help to supply free of charge to Government Health Departments of Third World countries, copies of up-to-date standard compendia such as, The Physician's Desk Reference (USA), the ABPI's Data Sheet Compendium (UK), the Rote Liste (Federal Republic of Germany) and the Dictionnaire Vidal (France).
3. The following procedure has been agreed to deal with alleged breaches in the observance of the Code. IFPMA Member Associations have been recommended to set up their own separate procedures for monitoring such complaints; many of the major Associations have already done this. A procedure has also been agreed to deal with complaints received by IFPMA itself and an ex officio committee of IFPMA's Council consisting of the President, the two

Vice-Presidents and the Executive Vice-President will oversee all IFPMA matters involving the Code.

The major sanction against any company that transgresses the Code will continue to be the sanction of adverse publicity. However, IFPMA wishes to stress that its main objective and that of its Member Associations will be to effect, as rapidly as possible, the correction of any proven breaches in the observance of the Code.

4. Comments have been made from time to time about the problem that industry faces in providing uniform information worldwide on labelling, packaging leaflets, data sheets and general advertising claims. The industry's position on the important matters of information on scientific claims, contra-indications and side effects is set out in the Code itself. This makes it clear that labelling, packaging leaflets, the information and data sheets and advertising claims should be consistent with the body of scientific and medical evidence pertaining to that product. This should be interpreted as meaning that such information given in Third World countries, should be consonant with what is being done in the companies' markets in the developed world. However, it should be borne in mind that countries which have their own regulatory procedures (and this includes many Third World countries) may well dictate a non-uniform approach to such matters, which industry has no option but to follow.

The voluntary adoption of this IFPMA Code is in line with one of the key objectives of the Federation as set out by its Founder Members in 1968, «to promote and support continuous development throughout the pharmaceutical industry of ethical principles and practices voluntarily agreed on».

Text of this Supplementary Statement in English only.

IFPMA Member Associations

Argentina

* Cámara Argentina de Especialidades Medicinales–CAEME
Suipacha 1380, 4° piso
1011 Buenos Aires, Argentina

Telephone 393-5577/5706/5978
Telex 23433

Australia

Australian Pharmaceutical Manufacturers Association–APMA
Level 14, AMP Centre
50 Bridge Street
Sydney 2000 N.S.W., Australia

Telephone 231 5377
Telex 26953 apmas
Cables apmasyd

Austria

Fachverband der Chemischen Industrie Österreichs
Gruppe Pharmazeutika
Bauernmarkt 13, Schliessfach Nr 69
A–1011 Vienna, Austria

Telephone 222 63 57 63
Telex 74 235 bks a

Belgium

Association Générale de l'Industrie du Médicament–AGIM
49, Square Marie-Louise
B–1040 Bruxelles 4, Belgium

Telephone 230 40 90
Telex 23167 fechim b
Cables fechimie

Bolivia

* Asociación de Industriales Quimico-Farmacéuticos de Bolivia–ALIFABOL
Cajón postal 8747
La Paz, Bolivia

Cables asinfarbo

Brazil

* Associação Brasileira da Industria Farmacêutica–ABIFARMA
Av. Beira Mar, 262-7° andar
CEP 20 021 Rio de Janeiro, Brazil

Telephone 224 1790
Cables abife

Canada

Pharmaceutical Manufacturers Association of Canada–
PMAC
141 Laurier Avenue West, Room 1110
Ottawa, Ontario K1P 5J3, Canada

Telephone 613 236-9993
Telex 53 3122 pmac ott

Central America

- FEDEFARMA–
  Federación Centroamericana de Laboratorios
  Farmacéuticos
  7a Av. 7-04–Zona 4
  Ciudad de Guatemala, Guatemala C.A.

  (representing pharmaceutical manufacturers of:
  Costa Rica, Guatemala, Honduras, Nicaragua, Panama,
  El Salvador)

Chile

- Cámara de la Industria Farmacéutica de Chile
  Agustinas 1022–Of. 427
  Casilla 13184, Correo 21
  Santiago, Chile

  Telephone 6 14 57

Colombia

- Asociación de Fabricantes de Productos Farmacéuticos–
  AFIDRO
  Transversal 6a, N° 27-10, 6° Piso
  Apartado aéreo 5461
  Bogotá, Colombia

  Telephone 34 15 80
  Telex 44 775 idro co
  Cables afidro

Denmark

MEFA–
Foreningen af Danske Medicinfabrikker
Landemaerket 25
DK-1119 Copenhagen K, Denmark

Telephone 11 12 70
Telex 16 370 mefa dk
Cables mefadex

Ecuador

- Asociación Profesional de Fabricantes y Distribuidores
  de la Industria Farmacéutica Ecuatoriana–
  ASOPROFAR
  P.O. Box 8842
  Ave. Eloy Alfaro 1824 y Bélgica
  Quito, Ecuador

  Telephone 453 503

Finland

Lääketeollisuusyhdistys r.y. (LTY)
Iso Roobertinkatu 4-6 A, P.O. Box 316
SF-00121 Helsinki 12, Finland

Telephone 90-66 18 71
Cables chemas

France

Syndicat National de l'Industrie Pharmaceutique
88, rue de la Faisanderie
F-75782 Paris Cedex 16, France

Telephone 1 503 21 01
Telex 612 828 snip f

Federal Republic of Germany

Bundesverband der Pharmazeutischen Industrie
Karlstrasse 21
D-6000 Frankfurt am Main 1, FRG

Telephone 611 255 60
Telex 412 718 bpi d
Cables pharmindustrie

Hong Kong

The Hong Kong Association of the Pharmaceutical Industry–
HKAPI
3B, 10/F. Hay Wah Building
72-86B, Lockhart Road, Wanchay
Hong Kong

Telephone 5-28 30 61
Cables pharmind

India

Organisation of Pharmaceutical Producers of India–
OPPI
Cook's Building
Dr Dadabhoy Naoroji Road
Bombay 400 001, India

Telephone 254 509
Cables oppind

Ireland

Federation of Irish Chemical Industries
13, Fitzwilliam Square
Dublin 2, Ireland

Telephone 01 765 116
Telex 33212 fici ei
Cables pharchem

Israel

Manufacturers' Association of Israel
Chemical and Pharmaceutical Division
Industry House, 29, Ha-Mered St.
P.O. Box 50022
Tel Aviv 61500, Israel

Telephone 650 121
Telex 342651 mais il
Cables mais

Italy

FARMINDUSTRIA
Piazza di Pietra 34
I-00186 Roma, Italy

Telephone 650 981
Telex 614281 farmin i

Japan

Japan Pharmaceutical Manufacturers Association
Amakasu Bldg
3-3 Nihonbashi Honcho, Chuo-ku
Tokyo 103, Japan

Telephone 241 0326

Korea

Korean Pharmaceutical Industry Association
19-20 Kwanchul Dong
Chongno-Ku
Seoul 110, South Korea

Telephone 74-1963/74-2401
Cables pharmassn

Malaysia

Malaysian Pharmaceutical Trade and Manufacturers
Association — MPTMA
31A, 1st Floor, Jalan SS 21/37
Damansara Utaman
Petaling Jaya, Selangor/Malaysia

Telephone 78754

Mexico

- Cámara Nacional de la Industria Farmacéutica-CANIFARMA
Av. Cuauhtémoc 1481
México 13, D.F., México

Telephone 534 60 70

Netherlands

NEFARMA–
Nederlandse Associatie van de Farmaceutische Industrie
Franciscusdreef 50, Postbus 9193
NL–3506 GD Utrecht, Netherlands

Telephone 030-62 14 44
Telex 40 969 nefar nl

New Zealand

Pharmaceutical Manufacturers' Association (New Zealand) Inc
8th Floor, Cumberland House
237–241 Willis Street, P.O. Box 27-041
Wellington 1, New Zealand

Telephone 845-382
Cables pharmanz

Norway

Norges Medisinalindustris Felleskontor–NOMI
P.O. Box 2937, Tøyen
Oslo 6, Norway

Telephone 19 25 00
Telex 18 151 weifa n
Cables nomidin

Pakistan

Pakistan Pharmaceutical Manufacturers Association–PPMA
130–131, Hotel Metropole
Club Road
Karachi, Pakistan

Telephone 511 773
Cables druglabs

Paraguay

* Asociación de Fabricantes de Productos Quimicos, Farmacéuticos y Afines
· Pte. Franco 570
Asunción, Paraguay

Peru

* Asociación Nacional de Laboratorios Farmacéuticos del Peru–ALAFARPE
Calle 41 N° 975 Urbanización Corpac
San Isidro
Lima 27, Peru

Telephone 40 97 90
Cables alafarpe

Philippines

Drug Association of the Philippines, Inc
P.O. Box 2248-MCC, Makati
Metro Manila, Philippines
Telephone 79 94 31

Portugal

Associação Portuguesa da Industria Farmacêutica–
APIFARMA
Avenida Duque de Avila, 95–2°
P–1000 Lisboa, Portugal

Telephone 4 12 48 / 54 45 70 / 53 03 91
Telex 16 529 apif p

Singapore

Singapore Association of Pharmaceutical Industries–
SAPI
Secretaries, Samas Pte Ltd
PO Box 3039
Singapore

Telephone 283 00 33
Telex 21 525 certify rs
Cables certified

South Africa

Pharmaceutical and Chemical Manufacturers' Association
of South Africa Limited
Showgrounds, Soutter Street
PO Box 933
Pretoria 0001, South Africa

Telephone 28-7348
Telex 3-0245 sa
Cables norfacts

Spain

FARMAINDUSTRIA
Fray Juan Gil, 5
Madrid (2), Spain

Telephone 250 3902 250 2426
Telex 46 995 find e

Sri Lanka

Sri Lanka Pharmaceutical Manufacturers Association
Chamber of Commerce Building
Post Box 274
Colombo, Sri Lanka

Telephone 21 745-47

Sweden

Lädemedelsindustriföreningen–LIF
Kungsgatan 32, P.O. Box 1319
S–111 83 Stockholm, Sweden

Telephone 8-24 13 70
Telex 17 947 swedrug
Cables lipharma

Switzerland

Swiss Society of Chemical Industries
Nordstrasse 15, P.O. Box 328
CH-8035 Zurich, Switzerland

Telephone 01-363 10 30
Telex 52 872 chimi ch
Cables chimisuisse

Turkey

Turkish Pharmaceutical Manufacturers Association
Zincirlikuyu Büyükdere Cad. 132/7
Istanbul

Telephone 67 68 31 – 67 68 33
Telex 26 282 fako tr

United Kingdom

The Association of the British Pharmaceutical Industry–
ABPI
12 Whitehall
London SW1A 2DY

Telephone 01-839 3961
Telex 298 916 abpi g
Cables pharmind london sw1

United States

Pharmaceutical Manufacturers Association–
PMA
1100 Fifteenth Street NW
Washington, DC 20005, USA

Telephone 202-835-3400
Telex 710 822 9494 pma wsh
Cables pharm

Uruguay

* Cámara de Especialidades Medicinales–
CUEME
Plaza Cagancha 1342, Piso 2, Esc. 9
Montevideo, Uruguay

Telephone 91 68 16 / 98 51 56

Venezuela

* Cámara de la Industria Farmacéutica Venezolana–
CIFAVE
Centro Profesional de Este
Piso 12-Of. 124/126
Caracas, Venezuela

Telephone 71 63 61

* Member of IFPMA through **FIFARMA**
Federación Latinoamericana de la Industria Farmacéutica
Venezuela (address as for CIFAVE above)

STATEMENT ON
THE PHARMACEUTICAL EXPORT AMENDMENTS
BY
MERCK & CO., INC.
SUBMITTED TO
THE SENATE LABOR AND HUMAN RESOURCES COMMITTEE

Merck & Co., Inc. is pleased to have an opportunity to submit a written statement in support of legislation to lift the export restriction on pharmaceutical products which have been approved for marketing in a foreign country, but which have not yet been approved for marketing in the United States. It is a matter of importance to our Company and to many other U.S. pharmaceutical companies; therefore, we appreciate the Committee's willingness to consider such legislation.

Merck is a major producer of prescription drugs and vaccines in the United States and throughout the world. The Company has more than 32,500 employees worldwide, about half of them in the United States. In 1984, Merck had total sales of $3.5 billion, predominantly in human and animal health care products. Approximately $1.5 billion, or 43% of these sales, were made by Merck subsidiaries located outside the United States. The current effective ban on the export of drugs that have not yet been approved by the FDA presents an impediment to the Company's ability to most efficiently utilize its existing manufacturing facilities in the United States. In addition, present law has the practical effect of preventing even consideration of construction of new or expanded facilities in the United States for a new product which will probably be first approved for marketing in a foreign country. It is for these reasons that Merck submits the following comments in support of a revision that would eliminate the existing export restriction.

I. Congress Never Intended the Impact of the Current Law.

It is clear that Congress did not intend to prohibit the export of products which comply with foreign laws. In fact, the Food, Drug and Cosmetic Act specifically provides for the export of a drug not approved under the Act under certain conditions.[1] The anomaly in the law is that, while such exports are allowed under one section, another section prohibits their introduction into interstate commerce.[2] Since interstate commerce has been interpreted to include commerce between the United States and a foreign country, exports are effectively prohibited.

A significant and, we are certain, unanticipated economic impact has resulted from the failure to conform these two provisions of the law. In order for a U.S. manufacturer to supply its international markets prior to receiving FDA approval, the U.S. law leaves a company no choice but to manufacture outside the United States. Though many foreign countries have pre-marketing approval requirements similar to those of the Food, Drug and Cosmetic Act, no other major drug producing country prohibits the export of new drugs approved in another country. In addition, new medications are usually approved more rapidly in foreign countries than in the United States. To remain competitive, drug products, once approved in foreign markets, must be available for worldwide marketing quickly. Delay could mean the loss of a crucial competitive edge.

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[1] Under Section 801(d) of the Food, Drug and Cosmetic Act, 21 USCA, a drug may be exported if it (1) accords to the specifications of the foreign purchaser; (2) is not in conflict with the laws of the country of import; (3) is labeled for export, and (4) is not sold or offered for sale in domestic commerce.

[2] Section 301(d) of the Food, Drug and Cosmetic Act prohibits "the introduction or delivery for introduction into interstate commerce of any article in violation of Section 404 or 505." (Section 505 provides for FDA approval of new drug applications (NDA) and Section 404 applies only to food products).

In its study issued in 1983, the National Academy of Engineering of the National Research Council found that there is "a clear relative deterioration in the foundation of (the U.S.) pharmaceutical competitive position." As one remedy to its finding, among others, the Council proposed "that exports of unlabeled chemicals for drug use abroad "should be allowed where a new drug application has not yet been approved" in the United States.[3]

II. Amendment of the Law Would Encourage Expansion of U.S. Plants.

Removing the export prohibition on drugs prior to FDA approval would encourage the retention and expansion of existing U.S. plants and the location of new facilities in this country, rather than abroad. An American manufacturer locating its production facilities in a foreign country need not rely on an approval for marketing in the host country in order to supply the needs of another country which may have approved the product first. For example, a manufacturer locating a new facility in the United Kingdom is assured that if the drug is first approved in France, the company's newly constructed or expanded plant facility in England could be made operational on a pre-determined and certain schedule to supply the French market.

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[3] "The Competitive Status of the U.S. Pharmaceutical Industry", NAS/NRC, 1983, p.1.

Once production goes overseas, jobs are often permanently lost to U.S. workers. Though not always the case, manufacturers will most likely utilize existing capacity in a foreign country before building new plants in this country. In the case of Merck, raw materials, not subject to the export restriction, for products sold overseas are manufactured in New Jersey, Pennsylvania, Virginia, Georgia, Puerto Rico, Great Britain, France, and Ireland, then shipped for further manufacture into bulk medicinals and finished products at facilities abroad. It is important to appreciate that the major portion of the value added during production occurs when tons of bulk raw materials are converted into kilograms of medicinal chemicals and then further processed into milligrams of finished product. So for drugs not yet approved by the FDA, current law prohibits the export of the more valuable bulk drug or finished product.

Merck, like other U.S. pharmaceutical manufacturers, has been denied the option of basing its total production of a new product in a single facility constructed in the U.S., from which it can supply both domestic and international markets. Instead, the company has necessarily had no choice but to construct facilities initially overseas, and then to build additional facilities in the United States when FDA approval of a new drug later is received here. This has often meant costly duplication of capital and manpower when a more economical alternative could have existed. Furthermore, in some cases existing U.S. capacity has gone underutilized as a result of this export restriction and, in one case Merck is now importing a Merck product from a plant built in England because of the consequences of the U.S. export prohibition.

As specific examples of the type of problems facing companies in our industry, we have selected two products that received approval for marketing outside the United States and then -- from three to five years later -- were approved in the United States.

Product	United Kingdom Approval	U.S. Approval
Dolobid	1977	1982
Ivermectin	1981	1984

DOLOBID (diflunisol) - Merck's Dolobid was first approved for marketing in the United Kingdom in 1977 but approval was not received in the United States until 1982. Because of export restrictions, production in the United States was limited to intermediates which could move in interstate commerce. In 1976, when initial production was begun in Virginia, Merck had sufficient manufacturing capacity there to meet its worldwide requirements for the finished product. Because of probable delay in receiving U.S. approval to market Dolobid, the decision was made to construct a chemical plant at Ponders End, England -- at a capital investment of $30 million -- to supply that product to our international markets. Over the past five years that plant has exported $46 million of this product to foreign markets and, for the past year, has been the source of supply for the U.S. market as well.

While there were other benefits from making such an investment in the United Kingdom, the fact remains that export restrictions imposed by the United States precluded even consideration of supplying the international markets from U.S. facilities. One consequence of this decision is that we now have existing manufacturing capacity in England which efficiency will dictate that we keep operating.

IVERMECTIN - Merck's experience with an animal health drug, Ivermectin, is illustrative of the problems engendered by export restrictions. Between 1980 and 1982, Merck made a $24 million capital investment in the construction of a major U.S. manufacturing facility in Puerto Rico, anticipating that once approval was received in the United States, the plant would supply worldwide demand for that drug.

U.S. approval of Ivermectin was expected in 1981, but was not received until 1983. Since Ivermectin was licensed in France, Holland and the United Kingdom in 1981, it was necessary to manufacture the product in England and Holland to supply those markets. As a result, there was significant underutilization of the plant in Puerto Rico for a considerable period of time.

MEFOXIN (cefoxitin) - In contrast, Merck's Mefoxin, an antibiotic not subject to a pre-approval export prohibition, was approved in Europe in early 1977 but not in the United States until late 1978. Because antibiotics may be exported under the existing export provisions of the Food, Drug & Cosmetic Act, Merck could supply foreign markets from a U.S. facility and, in fact, Mefoxin production facilities were built in the United States with the knowledge that we could anticipate full utilization of plant capacity even if FDA approval was inordinately delayed. Our plant in Elkton, Virginia, now supplies all of our international and domestic requirements. Approximately 200 employees at Elkton are directly involved with Mefoxin production and more than 100 more employees provide support services to the production people. Had we been required to construct a facility abroad to supply our initial foreign markets, chances are, we would still be using it for that purpose.

Similarly, Merck is now investing $100 million in the modification of existing facilities and construction of new facilities in New Jersey, Pennsylvania, and Virginia for the manufacture of a new antibiotic which has already been approved abroad but for which approval in the United States is not anticipated until later this year. Much of this is an investment Merck could not have considered making in this country without full knowledge that, even if FDA approval is substantially delayed, these facilities will not be idle because of an export restriction. About 100 new jobs directly related to the production of the new antibiotic will be created, in addition to those of construction workers needed to build the facilities and those of suppliers providing raw materials and services to the plants.

In recent years, hopes were raised that regulatory changes might reduce what has become known as the "drug lag" -- the extended period between submission of a product for regulatory review and its final approval in the United States compared with the shorter waiting period in Europe. We have no evidence that this lag is decreasing. For one important new entity we already have 15 foreign approvals but have not yet achieved U.S. approval.

Companies such as Merck will continue to face the problem of periodic underutilization of existing facilities if the drug approval period and the export restriction remain unchanged. At Merck's Rahway, New Jersey, manufacturing facilities, we will soon be faced with available and underutilized capacity. If new products approved overseas could be processed in part in these facilities more jobs could be maintained.

III. The Legislation Should Include Adequate Safeguards for Third World Countries.

Criticism of S. 2878 introduced in the 98th Congress has been voiced by those who believe that because of the demanding standards of the FDA, no drug should be exported unless FDA has determined it to be safe and effective for marketing in the U.S. There are those in other sophisticated countries who would vigorously object to the suggestion that they are not adequately equipped to protect the health and welfare of their own citizens.

It seems inappropriate, therefore, for a supplier of medicines to many nations to hold up any one country's medical judgment as a universal authority and withhold from other countries medicines that are deemed safe, effective and sometimes even essential, by international agencies and national governments.

Concern has been expressed over the safety and health of citizens in nations where only minimal safeguards exist. To meet these criticisms, S.2878 created safeguards for Third World countries which do not exist for products exported from any other country in the world.

For instance, the bill would have required FDA to establish a list of countries with adequate health regulatory agencies to approve drugs prior to marketing. It was anticipated that this would initially include a small number of countries. For instance, S. 2878 included Australia, Canada, France, Japan, Sweden, Switzerland, the United Kingdom, and West Germany. It is also well recognized that Belgium, Denmark, Ireland, the Netherlands and

Norway, to name a few, have highly sophisticated health regulatory agencies and we recommend that these be included in any legislation introduced this year. FDA could add to the list or subtract from it, where appropriate.

If a drug is not approved in the U.S., it would have to be approved in one of the countries listed by the Food and Drug Administration as having an adequate health regulatory authority to approve drugs. The proposal is consistent with Merck's longstanding practice to secure approval for new products from regulatory authorities in a medically sophisticated country prior to their introduction in any Third World markets. This practice reflects a recognition of the fact that Third World countries sometimes lack sufficient resources to set and enforce comprehensive rules for drug approval and distribution. Of course, all such exports would have to comply with the current Food, Drug and Cosmetic Act requirements of Section 801(d).

Among others, additional provisions to protect Third World countries required that:

1. The drug carry the labeling approved in a medically sophisticated country;
2. The drug not have been banned, withdrawn, or denied approval for reasons of safety or efficacy by final agency action of the FDA or by a health regulatory authority in a listed country;
3. FDA must have been notified of the intent to export to the unlisted country;
4. The drug must not have been the subject of a notice by FDA that its sale is contrary to the public health and safety of the country of

import. [This is to ensure that if there is a particular environmental or health condition in the country of import which makes the product dangerous to that country, FDA may require that the export be discontinued or prohibited at the outset].

All Third World countries have access to the same safety and efficacy information provided by drug companies for use to make approval decisions in developed nations. Some of them have approval agencies fully capable of acting in the best interest of their citizens. Others use an industrialized country as a surrogate regulator.

To assure that full and balanced information is distributed about our drugs, Merck has a disclosure policy that applies whether or not a product has been approved for sale in the United States. The cornerstone of our international disclosure system, the International Physicians Circular (IPC), is provided for each product we sell and comprises part of the initial submission to each national health authority in connection with application for marketing approval. Each IPC represents the company's best scientific judgment with respect to both the positive and negative aspects of our drugs, defining actions, indications, and dosage, as well as all warnings, contra-indications, precautions, and side-effects. These circulars, which are updated in a process of continuous medical review, serve to ensure globally consistent information about our products. In fact, Milton Silverman, in his book Prescriptions for Death: The Drugging of the Third World, concluded that Merck's "labeling throughout the world generally follows FDA guidelines..." and in a June 1982 interview with Time Magazine lauded Merck & Co. for "showing responsibility in labeling and promotion". In addition, quality control standards for manufacturing, storage and handling are consistent worldwide, regardless of less demanding importing country requirements.

IV. The Proposal Does Not Mean a Double Standard

The suggestion that the legislation would create a "double standard" distracts attention from the real issue. It ignores differences in countries' assessments of risk-benefit ratios, disease patterns, and tendencies in the practice of medicine even among culturally attuned countries. In fact, the European Community has labored unsuccessfully for years to develop a Community-wide drug approval mechanism. The best they have been able to come up with is agreement on basic protocols for approval. Yet patients in France, for example, take drugs approved by the French Government that are manufactured elsewhere in the Community but may not be approved in the country of origin.

The criteria for marketing in a country with an adequate approval mechanism are the standards that medical, regulatory, and pharmaceutical establishments within the country determine them to be. The location of manufacture is of no medical consequence--and should be of no legal consequence -- provided it meets the pharmaceutical specifications required by that country's authorities.

V. Impact on Exports to the Third World

We expect the proposal would have only a marginal impact on U.S. exports to developing countries. The major impact will be on exports to the developed countries of Europe and the Western Pacific which constitute--with the U.S. and Canada -- roughly three fourths of the world pharmaceutical market. By contrast, the developing countries make up about one-seventh of the world market with the Soviet Bloc countries taking up the balance. For Merck, sales to non-OECD countries -- primarily Third World nations -- amounted to a little more than approximately 8% of total 1984 turnover, representing only about one-quarter of sales to our OECD trading partners. A shifting of business to the Third World is highly unlikely and the legislation's impact would be substantially limited to OECD trade.

VI. Impact on Clinical Trials

It has been contended that changing the current drug export rules could give the impression that the U.S. is willing to allow drugs to be tested on people of other countries before being approved for use in the U.S. The legislation would effect no change on longstanding Merck policy and practice regarding clinical trials abroad. In addition to data from domestic clinical trials we use data from foreign countries in our INDs and NDAs as pivotal studies. We also use, when necessary, local studies sanctioned by local authorities to provide additional support for registration in each country or to gain post-marketing information. The protocols for international studies follow the same standard operating procedures used for domestic protocols.

Merck has conducted Phase I and Phase II testing in 21 countries. Non-OECD countries are chosen as clinical test sites only when the company is confident of the level of medical sophistication in a given national setting or, as in the case of Merck conducted clinical tests in Ghana, Liberia, Mali, and Senegal, to test a drug that appears to hold promise for the treatment of a tropical disease endemic only in less-developed countries.

Conclusion

o Any legislation should clearly protect the citizens of Third World countries. Passage of legislation similar to S. 2878 would enhance both the quality of products and the labeling information going to such countries and would provide adequate protection against so called "dumping" of disapproved products.

o Lifting the export restrictions on drugs approved in other countries would help strengthen America's position in world trade by removing artificial barriers that deny American manufacturers the option to locate a manufacturing facility in this country.

o Our laws should encourage exports, not inhibit them to the detriment of our own workers and our own economy. No other major industrial country in the world places its pharmaceutical manufacturers at such a disadvantage with regard to exports. The bill would remedy an unnecessary and inequitable restriction on American manufacturers while maintaining a high standard of quality, safety, and effectiveness that will enhance the competitive position of U.S. products in export markets.

We urge the Committee to favorably consider amending the Food, Drug and Cosmetic Act to accomplish these goals.

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IBA

Industrial Biotechnology Association
2115 East Jefferson Street
Rockville, Maryland 20852
Telephone: (301) 984-9598

Harvey S. Price
Executive Director

Directors
Officers
President
Ronald E. Cape
Cetus Corporation
Vice President
Gabriel Schmergel
Genetics Institute
Secretary
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Amgen
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Biogen
Robert A. Swanson
Genentech, Inc
Roger L. [illegible]
Damon Biotech

[illegible] -6 AM 5:[illegible]

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June 3, 1985

The Honorable Orrin G. Hatch
U.S. Senate
SR 135
Washington, D.C. 20510

Dear Senator Hatch:

On behalf of the commercial biotechnology community in the U.S., IBA would like to emphasize the need for near-term revision of U.S. export law concerning pharmaceutical products.

Presently, many new biotechnology companies are being solicited by other countries to set up manufacturing operations outside the U.S. This would result in loss of both jobs and technology at home, and weaken the U.S.'s international competitive position in an important commercial growth area. A major reason why such solicitations are enticing is that under present law, most important prescription drugs not yet approved by the FDA for use here may not be exported for commercial use to foreign countries which have approved them. This unreasonably limits market opportunities for young and innovative companies ready to commercialize pharmaceuticals, at a time when severe financial pressures threaten their existence. The present situation is thus detrimental both to our industry's future and to the U.S.'s future economic vitality.

To be sure, legitimate public policy concerns have been raised concerning shipment of unapproved drugs to the third world. We believe that the enclosed draft bill, which is similar to legislation that you introduced in the last session, is one approach which adequately addresses those concerns.

Surely, the U.S.'s current leadership in commercial biotechnology is a national asset of substantial value, which we would be foolish to squander. IBA hopes that this important issue can be resolved in the current session of Congress, and would be pleased to offer any further assistance to effect a reasonable result.

Sincerely,

HSP/td
Enclosures: IBA membership roster
Draft bill

A BILL

To amend the Federal Food, Drug, and Cosmetic Act to establish conditions for the export of drugs

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, That this Act may be cited as the "Pharmaceutical Export Amendments of 1985".

SEC.2. Section 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 381) is amended by adding at the end thereof the following new subsection:

"(e)(1) A drug (including a biological product) intended for human or animal use which --

"(A) requires approval by the Secretary under section 505 or section 512, or

"(B) requires licensing by the Secretary under section 351 of the Public Health Service Act or the Secretary of Agriculture under the Act of March 4, 1913 (known as the Virus Serum Toxin Act),

before it may be shipped in interstate commerce for export to a foreign country and which does not have such approval or license may, notwithstanding such section or Act, be shipped for export to a foreign country described in paragraph (2) if the drug meets the requirements of paragraph (3), or be shipped for export to any foreign country if the drug meets the requirements of paragraph (5).

"(2)(A) A foreign country to which a drug may be shipped for export under paragraph (1) if the drug meets the requirements of paragraph (3) is a foreign country included in the list established by the Secretary under subparagraph (B).

"(B)(i) The Secretary shall establish and keep current a list of foreign countries to which drugs may be shipped for export under subparagraph (A). In establishing and keeping current such list, the Secretary may, in his discretion, consult with experts in the field of drug regulation. The list of foreign countries to which such shipment for export is permitted shall include those foreign countries which are determined by the Secretary to have an adequate governmental health authority to approve drugs. To be listed, a foreign country must have both regulatory procedures sufficient to assure adequate scientific review of the animal and clinical studies relating to the safety and effectiveness of drugs before they are approved for marketing, and trained personnel with sufficient scientific knowledge and experience to implement those procedures. The initial list shall be established before the expiration of the ninety-day period beginning on the date of enactment of this subsection.. The Secretary shall provide a reasonable opportunity for public comment before the list is published.

"(ii) The Secretary shall add a foreign country to the list established under clause (i) if the Secretary determines the foreign country has an adequate governmental health authority to approve drugs, and the Secretary shall remove a foreign country from such list if the Secretary determines that the foreign country does not have an adequate governmental health authority to approve drugs. Any addition to or removal from the list shall be promulgated after an opportunity for public comment.

"(iii) At least once every two years the Secretary shall review the list established under clause (i) and consider whether action should be taken under clause (ii) to add or remove any foreign country.

"(3) A drug may be shipped for export under paragraph (1) to a foreign country included in the list established by the Secretary under paragraph (2) only if --

"(A) it is not the subject of final action by the Secretary or the Secretary of Agriculture denying, withdrawing, or suspending approval or licensing or otherwise banning the drug on the basis of safety or effectiveness;

"(B) it accords to the specifications of the foreign purchaser;

"(C) it is not in conflict with the laws of the country to which it is intended for export;

"(D) it is labeled on the outside of the shipping package that it is intended for export and is not approved for commercial marketing in the United States;

"(E) it has not been or is not introduced or offered for introduction into domestic commerce;

"(F) it is not the subject of a notice by the Secretary or the Secretary of Agriculture of a determination that the manufacture of the drug in the United States for export is contrary to public health and safety in the United States;

"(G) for a drug being shipped for export for any human use other than investigational use, there has been submitted to the Secretary and kept current an application for an exemption from the approval or licensing requirements described in paragraphs (1)(A) or (1)(B) for investigational use, or an application for approval or licensing, for a drug containing the same active ingredient or ingredients as the drug which is being shipped for export, except that for any such drug for which there is no significant market in the United States there may be submitted to the Secretary and kept current a master file containing all safety and effectiveness information required to be included in an application for an exemption from the approval or licensing requirements described in paragraphs (1)(A) or (1)(B) for investigational use of the drug;

"(H) the manufacturer or distributor of the drug has, at least ninety days prior to the date of first shipment of the drug to each foreign country, submitted to the Secretary or the Secretary of Agriculture a notification which contains the information prescribed by paragraph (4), and the Secretary or the Secretary of Agriculture has not determined such shipment to be unlawful under paragraph (4)(B). If the first shipment to a foreign country is solely for investigational use, a supplemental notification shall also be required at least 90 days prior to the first shipment for any human use other than for investigational use to demonstrate compliance with paragraph (3)(G), and the Secretary or the Secretary of Agriculture has not determined such shipment to be unlawful under paragraph (4)(B).

"(4)(A) the notification required under paragraph (3)(H) shall (i) identify the drug to be shipped for export, (ii) identify the establishment where it is to be manufactured for export, (iii) identify the foreign country or countries to which it is to be shipped, (iv) state that the requirements of paragraphs (3)(A) through (3)(C) have been met and will continue to be met, (v) state that the requirements of paragraphs (3)(D) through (3)(F) will be met, and (vi) if applicable, demonstrate that the requirement of paragraph (3)(G) has been met and state that such requirement will continue to be met.

"(B) The Secretary or the Secretary of Agriculture may determine, by written order within ninety days after the submission of the notification, that the proposed shipment for export is unlawful because such shipment does not meet all of the requirements of paragraph (3) or the notification does not meet all the requirements of paragraph (4)(A). Any such determination shall be accompanied by a written statement of the reasons therefor, shall specify any requirement of paragraph (3) that has not been met, and shall provide an opportunity for an informal hearing on the matter.

"(C) The Secretary or Secretary of Agriculture may at any time after such ninety days has expired determine, by written order, that any shipment for export is unlawful because such shipment does not meet all of the requirements of paragraph (3). Before any such determination is made because any of the requirements of paragraphs (3)(B) through (3)(F) is not met, the Secretary or Secretary of Agriculture shall notify in writing the person who submitted the notification of the preliminary determination that any such requirement is not met and shall provide thirty days within which such person may demonstate that any such requirement is met. If such demonstration is not made or is determined to be inadequate, or if the determination is based upon paragraph (3)(A) or (3)(G), the Secretary or Secretary of Agriculture shall by written order determine that the shipment for export is unlawful because such shipment does not meet all the requirements of paragraph (3), which shall be accompanied by a written statement of the reasons therefor, shall specify any requirement of paragraph (3) that has not been met, and shall provide an opportunity for an informal hearing on the matter.

"(5) A change in the labeling of a drug which has been approved or licensed as described in paragraphs (1)(A) or (1)(B) will not prevent its shipment for export with such labeling to any foreign country if the change is a translation or is a change made to meet the legal requirements of such country respecting information which does not relate to the safety or effectiveness of the drug and does not involve the addition of indications or other claims or the deletion or revision of warnings, contraindications, adverse reactions, or other similar information. The manufacturer or distributor shipping the drug for export under this paragraph (5) shall, before the first such shipment, obtain a written translation of such labeling in English and execute a written certification that such translation is a complete and accurate translation. Such translation and certification shall be retained by the manufacturer or distributor and shall be furnished to the Secretary upon request.

"(6) The Secretary shall establish procedures for --

"(A) periodically informing foreign governments of significant regulatory decisions, actions, and information respecting drugs in the United States;

"(B) periodically sending to foreign governments the required labeling for drugs approved or licensed by the Secretary or the Secretary of Agriculture; and

"(C) responding promptly to requests from foreign governments for available information on any drug imported from the United States.

Under such procedures no foreign government shall be furnished any information which is not available for public disclosure in the United States.

"(7) For the purpose of implementing and monitoring compliance with the requirements of this subsection, the Secretary shall enter into agreements with or utilize the services of any foreign government or United States embassy in a foreign country to obtain drug labeling used in any foreign country or drug safety or effectiveness information available in a foreign country."

SEC.3. The first list of foreign countries established by the Secretary of Health and Human Services under section 801(e)(2)(B)(i) of the Federal Food, Drug, and Cosmetic Act, as added by section 2 of the Pharmaceutical Export Amendments of 1985, shall include the following foreign countries unless such Secretary determines that one or more of such foreign countries does not have an adequate governmental health authority to approve drugs:

Australia
Belgium
Canada
Denmark
Federal Republic of Germany
France
Japan
Netherlands
Norway
Sweden
Switzerland
United Kingdom

STATEMENT ON
PROPOSALS TO PERMIT THE EXPORT OF DRUGS NOT APPROVED BY THE FDA

BY

RICHARD D. MILLER
RESEARCH ASSOCIATE OF THE LABOR INSTITUTE

SUBMITTED TO
THE SENATE COMMITTEE ON LABOR AND HUMAN RESOURCES
JUNE 5, 1985

On behalf of the Labor Institute, I am pleased to have an opportunity to submit a written statement examining some assumptions related to the proposal to lift the ban on the export of pharmaceuticals that have not been approved by the FDA. The Labor Institute is a New York City based education and economic research organization providing services to trade unions, national community groups and government agencies.

Proposed modifications to the Food, Drug and Cosmetic Act of 1938, which would permit the export of drugs not approved by the FDA, raises questions concerning domestic industrial policy on one level and responsible international health policy on the other. The commercial interests which serve to benefit from the export of unapproved drugs dominate the debate. Noticeably absent from the discussion is the voice of the Third World. Therefore, I am going to use a portion of this statement to communicate their message--using the words and language which expresses their concerns, verbatim--that exports of unapproved drugs represent an unacceptable threat to the health and welfare of Third World consumers. The domestic economic benefits from lifting the export ban are uncertain at best; and evaluating the claims of the drug industry require careful examination.

Economic Pressures to Relax Standards

Virtually all domestic industries, which export their products overseas, have been harmed by the strong dollar. The pharmaceutical industry, unfortunately, is no exception. The Commerce department predicts that the balance of trade in drugs and pharmaceuticals could be negative by the end of 1986, if current economic conditions persist. Moreover, there is an increasing trend of firms choosing to locate their R&D facilities overseas; in 1983 18.4% of the budgeted R&D expenditures of US firms were allocated overseas. In the current economic environment, proposals to permit the export of unapproved drugs seem superficially appealing. The drug industry promises that lifting the export ban will: (1) increase domestic employment; (2) create new tax revenues; (3) take some pressure off of the spiraling balance of trade deficit; (4) and stimulate domestic capital spending or utilize excess capacity. These assumptions will be examined below.

According to the Department of Commerce, the number of domestic production workers in the pharmaceutical industry will show a decline over the period from 1982-1985, even though the economy has been expanding. Is this a result of prohibitions against the export of unapproved drugs or are there other factors contributing to this decline? Commerce Department analyst Leo McIntyre has stated, "...multinational firms <have> switch<ed> from US to foreign production of many biologicals, medicinals, generic and brand-name preparations in order to compete in overseas markets." McIntyre explained that one reason R&D is going abroad, "...is to provide direct technical support for sales and manufacturing operations located overseas." If the strong dollar is responsible for declining employment and output in the drug industry, then a manufacturer would be foolish to ignore such a powerful disincentive to increase domestic production for export markets. Obviously, no executive regards the strong dollar as a trivial tax on the industry. Therefore, the promise of many new jobs resulting from producing unapproved exports is dubious at best.

Lured by tax holidays, low interest financing and low cost labor, virtually all drug firms have facilities located in Puerto Rico. In 1980, drug manufacturers enjoyed an average $58,743 tax savings per employee in Puerto Rico--far more than the average total wage costs for a stateside production worker! If new production operations were established to export an unapproved drug, lucrative off-shore incentives would point drug firms to this low tax environment. Value Line recently reported record EPS (earnings per share) for Merck & Co., due in part, "...to increased production in tax-sheltered Puerto Rico." Meanwhile Merck production workers are laid off in West Point, PA and Elkton, VA. Many other firms have expanded their operations in Puerto Rico over the last year. With such lucrative incentives to operate in Puerto Rico, it is unlikely that the Treasury will see significant tax revenues generated by lifting the export ban.

During the last round of Sec. 936 tax code debates, the drug industry argued that Puerto Rican operations train executives for expansion of US industry into Latin America. This implies that Puerto Rico provides a valuable industrial service: it can be used by the drug industry as a base from which to export more US pharmaceutical production worker jobs. On May 3, 1985, the Chairmen of SmithKline Beckman and Schering-Plough offered to set up operations in Grenada on the condition that Section 936 is retained in its present form by the Administration and Congress. Reportedly, Johnson & Johnson would establish a pilot facility in Grenada to finish production of surgical caps as part of a plan to link tax incentives to the Reagan Administration's Caribbean Basin Initiative. These caps would be finished from material initially prepared by workers at an expanded facility in Puerto Rico. Conclusion: drug firms are promising to export jobs overseas in exchange for keeping the current level of their tax shelter in place.

How do promises of increased job exports square with promises of more drug exports (and all of those promised jobs)? Which promises, if any, will the drug companies actually keep? Drug firms are complaining about idle capacity caused by export restrictions in one breath and simultaneously planning operations which serve to further idle their domestic capacity in the next. Costa Rica and El Salvador are also being considered as a co-production partners for Puerto Rican operations. There is no reason to believe that the promotion of the Caribbean Basin Initiative by the captains of the pharmaceutical industry is consistent with the objective of reducing the balance of trade deficit, increasing exports or stimulating domestic economic activity. I encourage the members of this committee to view the promises of the drug industry skeptically, to view this jobs-at-the-end-of-the-rainbow scheme cautiously--many factors can preclude the intended domestic economic benefits from lifting the ban on the export of drugs not approved by the FDA.

For further details on the job impacts I refer you to my study, published in the transcript of the July 27, 1984 hearings before the House Subcommittee on Health and the Environment. It details an order of magnitude estimate of new jobs potential from lifting the export ban--roughly 9 new domestic (stateside) production worker jobs/year for each of the top 35 pharmaceutical manufacturers. This estimate assumes the historical rate of NCE introductions, current tax policies, currency exchange rates and wage costs, and domestic content requirements of many nations. It assumes a sales per production worker of $400,000 per year, however this figure is dependent on current levels of productivity. As productivity increases, the marginal jobs impact of lifting the export ban declines.

A number of smaller bio-technology firms have argued that the drug export restriction limits their ability to compete with the large multinational pharmaceutical concerns. The large firms can easily circumvent the export restrictions by setting up overseas production facilities and marketing directly from their overseas operations. The smaller firms do not compete on a level playing field because they have limited access to resources. I believe that the concerns of these small firms are genuine, though perhaps somewhat overstated. Most small biotech firms rely upon large multinational drug firms to produce and market their products overseas. The costs which prohibit duplicate overseas production facilities also limit the ability of biotech firms to establish overseas 'detailing' and marketing operations. For example, it is widely known that Genentech, a California biotech firm, has set up a joint venture with Hoffman LaRoche. Since most emerging biotech firms rely upon joint ventures and licensing arrangements, the production limitations for overseas markets is perhaps overstated.

Voices from the Third World

The domestic economic benefits, which would result from lifting the export ban, need to be weighed against the risks and potential costs which will affect foreigners and Americans traveling abroad. Particularly vulnerable are those consumers in the Third World whose health care delivery systems are extremely limited; where adverse reactions to a drug are difficult to trace and report; and where pharmaceutical manufacturers are relatively immune from liability in the event a drug has inflicted harm. The concerns of those who provide health care services in the Third World are expressed below--their concerns are practical rather than ideological.

The Coordinating Committee for Primary Health Care of Thai Non-Governmental Organizations represents 16 Health-Development Organizations. It objects to the export of unapproved drugs for several reasons:

> 1. "...it goes against the 'Universal Declaration of Human Rights' because it allows the existence of a 'double standard' of drugs."
>
> 2. "...is contrary of the appeal of the WHO to all countries all over the world to develop quality of life by means of primary health care and to achieve <the> goal of health for all by the year 2000. ...the WHO has prepared the 'Essential Drugs List' which consists of about 200 kinds of drug that are approved by experts to be sufficient for curing and healing most of diseases that catch people in most countries. Now, the developing countries are inundated <with> unqualified pharmaceuticals. <In> Thailand there are more than 22,000 formulas which about 46% of them are unqualified compound pharmacopoeias. Therefore, the legislation which allows export of unapproved drugs in USA will distinctly contravene the purpose of WHO."
>
> 3. "The proposal will cause more problems to Thailand's

drug consumption; now, Thai people are imposed to use 'double standard' drugs, drugs that are labeled 'For Export Only', drugs that are on-trial and drugs that have been already banned, because the exporters and manufacturers employ various tactics, even give insufficient or untrue information, to make our drug approval authorities accept the products unwittingly."

"Such proposal of the US drug industry will worsen the situation of drug consumption in Thailand, will increase the risk in drug toxicity of people; thus it will support the process of health destruction."

The letter was closed with the following appeal:

"The USA has been our good friendly nation for a long time, we are hopeful that the just scrutiny upon such proposal will prove again (your) cordiality to the Thai nation and people."

ALIRAN is a human rights organization located in Penang, Malaysia. Dr. Chandra Muzaffar, President of ALIRAN, voiced the concern of his human rights and justice organization with respect to the drug export bill:

"It is a move which will discredit not only the multinational companies involved in this exercise, but also the United States government. The United States government should not give the 'green light' to what amounts to blatant exploitation of the Third World by greedy commercial enterprises."

The Catholic Commission for Evangelization, Justice and Development is the organ of the New Zealand Catholics Bishops Conference responsible for its program of overseas development and local and international justice and peace issues. David Mahoney offered the following comments:

"Our practical understanding of the living situation of the poor of Asia and the Pacific, in particular, make us view with considerable alarm and strong opposition proposals to allow the export to the Third World, drugs not yet approved by the FDA. The way to enhance and uphold the dignity of of the people of the Third World is to allow them, at minimum, the same protection and quality in benefitting from the technological advancements in medicine, as you grant to your own people. To have lower standards is, at best paternalistic and belittling of their human dignity, and at

> worse, to use people of the Third World as human Guinea Pigs."
>
> "To have people claim that Third World governments can decide <which drugs are safe> is viewed as no more than a spurious and callous attempt to deny the people of the Third World the protection and safeguards that you consider necessary for your own citizens."

The Catholic Hospital Association of India represents nearly 2000 health care institutions in India under the auspices of the Catholic Church. Fr. John Vattamattom SVD, the executive director, expressed shock and concern over unapproved exports:

> "We are deeply concerned on this issue, and we feel painfully that once this proposal is passed, <it will> seriously damage the health of Third World customers."

Satyodaya is a Non-governmental organization located in the city of Kandy in Sri Lanka. It is deeply involved in safe-guarding the health of two sectors of the population: workers on the plantations and the rural peasantry of the Kandy region. In the past the latter have been victims of colonial exploitation and are among the most malnourished of the country.

> "We view these proposals with deep concern and anxiety. If the present laws are relaxed to permit the exportation of such drugs, it would mean that Third World countries, such as ours, will be the dumping grounds for drugs of dubious standards and of potential danger to the health and safety of our people."

On December 3, 1984 hundreds of Thai pharmacology students demonstrated outside the US embassy in Bangkok. They were protesting against the 1984 Pharmaceutical Export Amendment (S. 2878) because it would make it easier for American drug manufacturers to export unapproved products to the Third World. On December 5, the South China Morning Post reported that students were carrying signs saying:

> "...'we protest the inhuman double standard policy of the

US,' and 'Thailand is not a dumping ground for your garbage.'"

"The Assistant Secretary General of the Thai Public Health Ministry for Food and Drugs, Mr. Tri Sangthongtong, said the 'students have every right to stage the protest, but we don't want to let ourselves become involved in the matter.'"

"He added: 'However, it must be remembered that the Thais are not laboratory rats to be used for testing medicines.'"

Policy Considerations

I would encourage the committee staff to weigh the estimable, and relatively minor economic benefits of exporting drugs not approved by the FDA against the clear and unambiguous rejection of the proposal by those who deliver health care services in the Third World. Furthermore, I would encourage the committee to invite comments from a broad range of Third World governmental and non-governmental health care agencies to ascertain what is in the best interests of Third World consumers. Those peoples, who will suffer the costs of consuming drugs whose safety and efficacy has been not been ascertained by the FDA, must be considered in this debate. Until they are satisfied that adequate safeguards have been built into the drug export proposal, it remains flawed and unacceptable.

It has been suggested that exports be limited to those industrialized countries which have effective means to regulate the import, marketing and labeling of drugs. While this proposal eliminates the politically infeasible problem of determining which countries have an "adequate health authority" as determined by the Secretary of HHS (which was proposed in S. 2878), it creates a new one in turn. If exports of drugs, which have not been approved by the FDA, are made to industrialized countries, the potential for re-export presents a real problem. There are no mechanisms to prevent the re-export of these products to Third World countries. Labeling requirements, which might say "For Export to 'XYZ' OECD Country Only", are insufficient safeguards, since relabeling or repackaging is always an option for a manufacturer--as long as Third World markets provide profitable opportunities. Under the OECD-country-only scenario, the only change is that an industrialized importing country becomes a middle-man for reshipments to the Third World. Moreover, this presents a situation where the drug industry is free to exploit lower export standards present elsewhere while producing where the regulatory standards are higher.

To reiterate, a drug export bill which limits unapproved exports to Europe or the OECD countries is strictly cosmetic. This 'modification' to S. 2878, (submitted in July of 1984 by Senators Hatch and Quayle) is neither a compromise nor an alternative. Furthermore, it in no way addresses the concerns raised earlier in this statement by Third World health workers and consumers.

Considering that the 'drug lag' is responsible for stimulating the drug export question in the first place, perhaps the responsible policy would be to encourage European countries to raise their standards on drug exports. By doing so, we would be encouraging a level playing field for both US and foreign drug producers. This appears to be sensible policy--at least until the developing world can cope with the prowess of the multinational pharmaceutical industry.

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Statement of

Ambassador Michael B. Smith
Acting United States Trade Representative
Office of the United States Trade Representative

Before the

Senate Committee on Labor and Human Resources
United States Senate

June 5, 1985

on

An Amendment to the Food Drug and Cosmetic Act
to permit the export of unapproved new drugs

Mr. Chairman, and members of the Committee, I appreciate this opportunity to discuss the trade policy impact of the current prohibition on the export of unapproved new drugs to foreign countries that have already approved them.

The United States is experiencing significant and growing merchandise trade deficits. In 1984, our merchandise trade deficit more than doubled from the preceding year to a total of $124 billion. It is estimated that in 1985, the trade deficit may rise to between $140 and $160 billlion. Of even greater significance is the rapid deterioration in our balance of payments. Our payments deficit increased from $42 billion in 1983 to over $100 billion in 1984. Essentially, this means that America borrowed slightly over $100 billion from foreign sources last year and had a goods and services trade deficit of like amount. The United States is expected to become the biggest debtor nation in the world by the end of this year. If deficits of this magnitude continue to accumulate, the American living standard must decline because of the heavy servicing of foreign debts we will face.

While our weak trade performance is largely due to the strong dollar, a substantial contributing element is the imposition by the U.S. Government of a broad array of disincentives in the path of our exporters. While the effect of these disincentives is difficult to quantify, it is clearly substantial. By inhibiting our exports, these disincentives have significant adverse economic effects. Further, U.S. disincentives particularly impact sales of the high technology and small business sectors, areas where we ought to be doing everything possible to increase our competitiveness, not weaken it.

Other nations strongly support their export sectors. Not only do they do more proportionately to promote exports than does the United States, but they do not impose extensive disincentives to exports. The net result of this situation is that world production patterns are distorted, to our nation's detriment, from what would be the result of market forces.

One of these export disincentives--the new drug and biological export prohibition-- is unique to the United States: no other nation prohibits the export of drugs to countries that have approved these drugs. I would like to address this issue in the context of two key trends that will affect world trade for the rest of the century. The first is the growing economic interdependence of nations, as evidenced by the dramatic growth in world trade. The second is the accelerating pace of technological change.

In 1960, world output (GNP) was $5.5 trillion and world exports were $139 billion, or 2.5 percent of world GNP. By 1981, world output had increased to $13.5 trillion and world exports to $2 trillion, or 15 percent of world GNP. During this same period, U.S. exports doubled as a percentage of U.S. GNP, from 4 percent to 8 percent. Today, 5 million American jobs are dependent on exports.

In contrast with the consecutive and growing trade deficits the United States has incurred since 1977, the U.S. drug industry has consistently shown a sizable trade surplus. However, the size of this surplus is rapidly shrinking. In 1982, our drug trade surplus was $1.2 billion; the Department of Commerce projects that this surplus will decline to $825 million in 1985. According to the U.S. Industrial Outlook, the value of U.S. pharmaceuticals exports was an estimated $2.7 billion in 1984, an increase of

6.5 percent, while imports rose to $1.8 billion, up 35 percent. The Commerce Department projects that if this trend continues, the balance of trade in such products will be negative by the end of 1986. While part of the reason for this trend is the strong dollar, the U.S. Industrial Outlook cites the current ban on the export of drugs not approved for sale in the United States as an additional factor, pointing out that drugs that have been developed in the United States but not yet approved by the Food and Drug Administration (FDA) must be produced abroad if they are to be sold abroad.

Some $8-$10 billion per year of foreign drug sales by U.S. companies are accounted for by their foreign subsidaries. A large portion, perhaps most, of these sales would have been supplied by exports from the United States if this had been permitted by U.S. law. Most of the technology in these drugs is now widely available. However, the industry estimates that an incremental $400 to $500 million in additional exports would be generated from new drugs products by the fifth year after amendment of the law. The export potential for future high technology drugs, including biotechnology products, could be several times this amount. Should the law not be amended, the industry estimates that over the next several years, our restrictions on exports could result in an additional incremental loss of $400 million in capital investment and a loss of 8 to 10 thousand job opportunities.

The second trend that I mentioned before that will significantly impact world trade for the rest of this century is the accelerating pace of technological change. The total body of human knowledge is expected to double in the next twenty years. Life cycles of commercial products will continue to shorten due to this fact. It currently takes 6 to 8 years to obtain regulatory approval of a new drug in the United States. The lengthly regulatory approval process coupled with the export prohibition and shorter product life cycles will provide even greater incentives for American pharmaceutical companies to locate manufacturing facilities abroad.

It is also important to note that a decision to move manufacturing facilities overseas carries with it a necessity to provide direct technical support for such facilities. Thus, we must anticipate that an increasing proportion of Research and Development (R & D) expenditures of pharmaceutical firms will be made abroad because of the factors I have enumerated. These trends are already becoming evident. In 1984, U.S. pharmaceutical firms spent around $650 million abroad for R & D. And these foreign R & D expenditures are increasing at a rate of 17 percent a year, which is somewhat higher than the projected rate of domestic increase. The Commerce Department estimates that total U.S. pharmaceutical industry R & D expenditures could reach $7.5 billion by 1989, of which $1.25 billion would be for research done in by 1989, of which $1.25 billion would be for research done in U.S. owned R & D facilities abroad.

The United States has traditionally enjoyed a trade advantage in high technology goods, such as pharmaceuticals. The trend toward increased R & D abroad, combined with foreign manufacturing, is alarming. America is losing its competitive advantage in an important sector of high technology precisely at a time when we are becoming more dependent on exports. We are witnessing: the transfer of technology out of the United States, lost employment opportunities for U.S. workers, lost capital investment in the United States, and lost opportunity to improve the balance of trade. The drug export prohibition is a significant reason for these trends. And we see no possibility of significantly altering this situation as long as the present export prohibition law remains unchanged.

We can expect to see all of these conditions apply to the important emerging field of biotechnology. But with an additional fact--large companies may have facilities in foreign countries; small companies do not have and probably cannot afford to establish such facilities. These are precisely the companies that are producing many of the innovative breakthroughs in biotechnology, and thus constitute the leading edge of our high technology competitiveness. The options for these small companies are limited--they can choose not to compete or they can license their technology and knowhow and run the risk of "selling their seed corn." This bodes ill for future U.S. competitiveness.

Mr. Chairman the export of unapproved pharmaceuticals and biological substances, with adequate safeguards, is commercially intelligent and fully consistent with the General Agreement on Tariffs and Trade (GATT).

I wish to emphasize that once legislation is drafted for consideration, the Office of the U.S. Trade Representative will defer to the Department of Health and Human Services for the Administration's assessment of whatever health safeguards are deemed necessary in connection with such exports.

We urge you to take the necessary actions to amend the Food, Drug and Cosmetics Act and the Public Health Services Act to allow the export of drugs and biologicals to countries where they can be lawfully marketed. By taking this step, the United States can improve its trade balance, generate jobs for Americans, stimulate greater R & D spending at home, and strengthen America's industrial base.

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

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INSTITUTE FOR HEALTH POLICY STUDIES
SCHOOL OF MEDICINE
1326 THIRD AVENUE
SAN FRANCISCO, CALIFORNIA 94143

June 3, 1985

The Honorable Orrin G. Hatch
Chairman
Committee on Labor and Human Resources
United States Senate
Washington, DC 20510

Dear Mr. Chairman:

In response to requests by staff of the Committee on Labor and Human Resources, U.S. Senate, we are pleased to comment on possible legislation with respect to the export of drugs not approved in the United States, specifically proposals to modify Section 801 of the Food, Drug and Cosmetic Act (21 U.S.C. 381). Although we recognize that no specific legislation is currently before the Committee, we are providing comments on the proposed draft amendments to the Food, Drug and Cosmetic Act, dated December 26, 1984.

As two individuals who have been involved in the study of federal drug policies for the past 20 years, we are basing our comments on our own studies and on a review of the work of others. In a letter from Dr. Lee to Chairman Hatch dated June 22, 1984 (attached), a brief history of our testimony before the Senate as well as our research and the resulting publications were described. In addition, we noted our participation in a number of other activities relating to prescription drug policies.

In the past we have opposed all legislation proposing amendments to the Food, Drug and Cosmetic Act that would permit the export of drugs not approved for use in the United States. In view of the developments in biotechnology in the United States and in Europe during the past decade and the improvements in drug regulatory systems in European countries, Canada, Japan, Australia and New Zealand in the past decade, we would now support such legislation if it were properly drafted. We do not approve the draft of December 26, 1984 as it currently stands, but believe if sufficient changes were made it could be acceptable. In this letter we will comment both on the language of the December 26, 1984 draft and on what we believe should be the intent of acceptable legislation. We will comment on a section-by-section basis, referring both to the draft that was sent to us and the analysis entitled "Pharmaceutical Export Amendments of 1985, December 26, 1984" that was sent with a copy of the proposed draft legislation.

Section 2

Paragraph (e)(1) defines the drugs (including biological products) that may be exported under the proposed amendments.

The export provisions of the proposed amendments are limited to those drugs which under current law are prohibited for export because they have not been approved or licensed for interstate distribution. The amendment applies to drugs for both human and animal use and it includes biological products and nonbiological products.

The proposed export provisions do not apply to antibiotic drugs for human use or to any other drug presently allowed to be exported under Section 801 (d)(1) of the Food, Drug and Cosmetic Act. This is a serious omission because there are major problems associated with the labeling, marketing, and use of antibiotics, including those exported to Third World countries by U.S. pharmaceutical manufacturers, as well as by other antibiotic manufacturers throughout the world.

In testimony submitted to the Committee on Labor and Human Resources dated June 22, 1984, a detailed analysis of the problems relating to antibiotics was presented. We believe that this analysis is still applicable, and we believe that antibiotics should be included within the proposed legislation.

The second problem with Section (e)(1) is that its definition of drugs is too broad. We believe the problem in the United States relates primarily to commercial biotechnology drug products and, if possible, the legislation should be drafted to deal with that specific problem rather than be as all-encompassing as the December 26 draft. We would include within the provisions of the law those drug products that would be included within the definition of commercial biotechnology as defined by the Office of Technology Assessment, U.S. Congress, in a report published by OTA in 1984 (Commercial Biotechnology --An International Analysis, Washington, D.C., Office of Technology Assessment, U.S. Congress OTA-BA-218, January 1984). We believe there are serious problems related to the export of biotechnology products, a number of which were identified in a memorandum dated April 29, 1985 addressed to the Honorable Edward M. Kennedy, U.S. Senate, by Genentech. These could be addressed if the legislation dealt with biotechnology drugs and biologics, rather than all drugs.

Paragraphs (e)(2)(a) and (b) and (c) define the countries to which a drug may be exported.

These sections identify those countries to which drugs not approved for use in the United States can be exported, including those on a list of countries "determined by the Secretary to have an adequate governmental health authority to approve drugs." It is stipulated that "the Secretary shall add a foreign country to the list established under clause (i) if the Secretary determines the foreign country has an adequate governmental health authority to approve drugs, and the Secretary shall remove a foreign country from such a list if the Secretary determines that the foreign country does not have an adequate governmental health authority to approve drugs. Any addition to or removal from the list shall be promulgated after an opportunity for public comment."

The provisions in these sections are too vague. Congress should be more specific in its instructions with respect to the criteria for determining what is and what is not "an adequate governmental authority to approve drugs." It is one thing to have a governmental authority to approve drugs; it may be quite another to have a governmental agency to effectively administer laws that regulate both the safety and effectiveness of drugs. Laws are effective only if they are implemented effectively. We found the language in the analysis ("Pharmaceutical Export Amendments of 1985, December 26, 1984") that accompanied the proposed amendments helpful in clarifying Congressional intent. Particularly useful was the sentence: "To be listed, a foreign country must have both regulatory procedures sufficient to assure adequate scientific review of animal and clinical studies relating to the safety and effectiveness of drugs before they are approved and trained personnel with sufficient scientific knowledge and experience to implement those procedures." We believe that this language should be included in the legislation. However, it must also be recognized that although a number of countries, particularly those in the Third World, have such laws on their books, their implementation of the laws is totally ineffective, or only modestly effective, thus providing little assurance for physicians, pharmacists or patients that the drugs on the market will be safe or effective.

Another important requirement for any drug regulatory agency to be approved would be provisions relating to the regulation of drug product labeling, including patient package inserts, and of promotion and advertising practices aimed at physicians, pharmacists and the general public.

Paragraph (e)(3) further defines the conditions for export of drugs not approved for use in the United States.

This paragraph sets forth eight conditions which any unapproved drug must meet before it can be exported to a listed foreign country.

First, the drug must not be the subject of final action by the Secretary of Health and Human Services or the Secretary of Agriculture denying, withdrawing or suspending approval or licensing or otherwise banning the drug. We would add to this section language which would include drugs that are voluntarily withdrawn from the market by the manufacturer for reasons of safety or effectiveness.

Second, the drug must be in accord with the specifications of the foreign purchaser. We are in agreement.

Third, the drug must not be in conflict with the laws of the country to which it is intended for export. We would substitute that the drug must be approved for use under the laws of the country to which it is intended for export.

Fourth, the drug must be labeled on the outside of the shipping package that it is intended for export and that it is not approved for commercial marketing in the United States. We would add that such information also must be included in the container labeling (the package insert) and in advertising or other promotional materials for physicians, pharmacists, dentists and consumers.

Fifth, the drug must not have been and must not be introduced or offered for introduction into domestic commerce. We would add: "in the United States."

Sixth, the drug must not be the subject of a notice by the Secretary of Health and Human Services or the Secretary of Agriculture determining that manufacture of the drug in the United States for export presents a significant risk to the public's health and safety in the United States. We are in agreement.

Seventh, for any drug shipped to a foreign country for human or other than investigational use, there must be submitted to the Department of Health and Human Services and kept current an application for investigational use exemption or an application for approval or licensing in the case of a drug containing the same active ingredient or ingredients as the drug being shipped for export; for a drug which has no significant market in the United States there must be a master file which includes all the safety and effectiveness information required for an application for the investigational use exemption for the drug. This section really has two separate purposes and we believe they should be separated. First, we believe that for drugs that are potentially for use in the United States as well as in Europe, Canada, Japan, Australia and New Zealand, Phase I testing under an IND should be completed and Phase II testing initiated. The company proposing to export the drug should maintain a good-faith effort to complete testing under the investigational use exemption and should then proceed with a new drug application. •Because a variety of factors affect this process, we would not set a time deadline on that, but it is an issue that should be addressed in the legislation.

Eighth, the drug must be subject to a notification submitted to the Department of Health and Human Services and the Department of Agriculture at least 90 days prior to the date of first shipment to each foreign country. We would agree with this requirement, but we believe there should be a public hearing with respect to export; whether it is appropriate in this section or in another section would clearly be for the committee to decide. In addition, we believe that an affirmative action should be required by the Department of Health and Human Services for a drug to be exported, not simply an action to disapprove export. Perhaps the requirement would be better included under Section (e)(4) rather than Section (e)(3).

There is another problem that is not adequately addressed in the draft amendments and that has not been adequately addressed in previous proposals relating to the export of drugs not approved for use in the United States. This is the problem of drugs used to treat vector-borne diseases that are rarely found in Western industrialized nations, such as malaria, Chagas' disease, trypanosomiasis (sleeping sickness), schistosomiasis (bilharziasis) and onchocerciasis (river blindness). We do not have specific language that would correct this problem, but we believe it is an important problem that relates primarily to export of drugs to the Third World and not to the European countries on the proposed list that are included under Section 3.

Paragraph (e)(4) establishes the contents and procedures for the export notification required under Paragraph (3)(H).

We would in general concur with these requirements.

Paragraph (e)(5) relates to labeling of a drug which has been approved or licensed.

In general, we agree with these provisions but recall that the Food and Drug Administration raised some issues in their testimony last year, and they should be consulted with respect to this section.

Paragraph (e)(6) relates to procedures that the Secretary shall establish for periodically informing foreign governments of significant regulatory decisions, actions, and information respecting drugs in the United States; sending materials to foreign governments with respect to labeling; and responding to requests for information.

We concur with these recommendations.

Paragraph (e)(7) requires the Secretary to enter into agreements with or otherwise use the services of a foreign government and the United States embassies in order to implement and monitor compliance with the requirements of this subsection.

We agree with this, but we believe that an independent monitoring system should be established to monitor compliance. We also believe that there should be a provision for studies in European countries, Japan, Canada, Australia, New Zealand and in the Third World.

It is critically important that the law prohibit the secondary export of drugs to other countries from the country to which it is exported. In order to assure that, an effective monitoring system is needed, and we do not believe that the system described in Paragraph (e)(7) is adequate for that purpose.

Section 3

This section includes a list of countries with adequate regulatory systems to which drugs not approved for use in the United States may be exported under the provisions of this law. We would add Finland and New Zealand to the initial list.

In summary, while we would support legislation designed to permit the export of drugs not approved for use in the United States to selected countries in Europe and North America, as well as Japan, New Zealand and Australia, we believe that the draft proposals do not provide adequate protections. Therefore, we have suggested modifications that we believe would make the amendments acceptable and would accomplish the purposes of the legislation.

Sincerely,

Philip R. Lee, M.D.
Professor of Social Medicine

Milton Silverman, Ph.D.
Research Pharmacologist Emeritus

attachment

/lg

POSITION OF AMERICAN CYANAMID COMPANY

RESTRICTIONS ON PHARMACEUTICAL EXPORTS

ISSUE: Whether the current ban under U.S. laws and regulations should be lifted to permit exports of human and animal drugs and biologicals approved abroad prior to receiving approval by the Food & Drug Administration.

CYANAMID INTEREST: Current laws and regulations put American Cyanamid and other companies in the position of having to build new facilities overseas to produce human and animal drugs and biologicals that are approved abroad before they are approved in the United States. Although many factors affect decisions for locating production facilities, the export ban automatically precludes any consideration of locating them in the United States. Jobs, investment, technology and favorable balance of trade surpluses are lost to the U.S. since Cyanamid and other companies are forced to export the means of production rather than the product itself.

BACKGROUND: The Federal Food, Drug & Cosmetic Act and the Public Health Service Act are interpreted by the Food and Drug Administration to require new animal and human drugs and biologicals to be approved in the U.S. by the FDA before they can be exported.

Of all major drug exporting nations -- the United Stated, Japan, West Germany, France, Italy and the United Kingdom -- only the United States imposes such a ban on the export of drugs approved by the importing nation before they have been approved by the producing country. This is important because it takes approximately seven to ten years to develop new products and gain U.S. approval. Thus, they are usually introduced abroad before they are introduced in the United States.

Today, Cyanamid has several new drugs in, or about to begin, clinical testing for U.S. approval. Under existing laws and regulations, all of these must first be approved by the FDA before they can be exported. This is regardless of the need overseas or the willingness of foreign health authorities, with their own registration procedures, to approve the drugs for their countries.

Many pharmaceutical manufacturers are now considering where to build research and manufacturing facilities to produce new medicines by recombinant DNA techniques. Because manufacturers can anticipate that the products of that new technology will be approved for marketing in other countries before they are approved in the United States, they have strong incentives to locate their principal facilities abroad. What is at stake is not only the preservation of American jobs and capital investments, but the nation's commanding early lead in the recombinant DNA field. If the research and manufacturing base shifts to other countries, important technical expertise will flow with it.

The rationale behind the export ban is based on the premise that, unless so restricted, multinational pharmaceutical companies will "dump" dangerous drugs overseas, particularly on unsuspecting third world countries which lack the sophistication to evaluate new drug compounds. There are a number of serious flaws in that theory.

First, the major marketing thrust of most U.S. multinational pharmaceutical companies is in the developed countries. Each has its own board of health which sets rigorous procedures for evaluating new drugs.

Second, most developing countries that lack a board of health skilled in drug evaluation adopt the decisions of those countries which do have sophisticated regulatory agencies. They require "Free Sale Certificates" for drug imports which protects them by requiring the sale of any drug to be first approved by at least one major developed country -- thus fulfilling the role of the FDA.

Finally, the underlying goal of "protecting" third world countries is irrelevant since the products can be manufactured outside the United States and sold to them anyway.

CYANAMID POSITION: American Cyanamid recommends changes in current laws to permit export of investigational and commercial quantities of human and animal drugs and biologicals approved overseas but not in the U.S.

The **Chairman**. The hearing is now adjourned.

[Whereupon, at 1:23 p.m., the committee adjourned, subject to the call of the Chair.]

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